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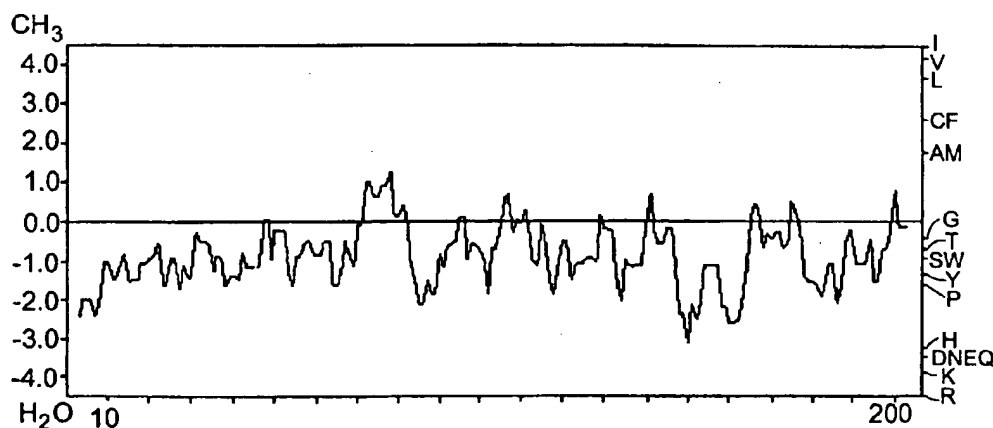
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(54) Title: **ANGIOPOETIN RELATED FACTORS**



(57) Abstract: The invention provides fusion proteins comprising a fibrinogen-like domain comprising an amino acid sequence identical or homologous to the amino acid sequence of the fibrinogen-like domain of a first wild-type angiopoietin-related factor and a coiled-coil domain comprising an amino acid sequence identical or homologous to the coiled-coil domain of a second wild-type angiopoietin-related factor, where the first and second wild-type angiopoietin related factors are different. The invention further provides polynucleotides encoding such fusion proteins, vectors comprising such polynucleotides, and methods of making and administering such fusion proteins, polynucleotides, and vectors.

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## ANGIOPOIETIN RELATED FACTORS

## FIELD OF THE INVENTION

[0001] This invention pertains to novel angiopoietin related factors, nucleic acids encoding such factors, vectors comprising such nucleic acids, and methods of producing and administering such factors, nucleic acids, and vectors.

## BACKGROUND OF THE INVENTION

[0002] The angiopoietins are a recently discovered family of related proteins. Angiopoietins are characterized by their ability to bind Tie receptors (sometimes also referred to as “ork” or “tek” receptors) (described in, e.g., International Patent Application WO 98/05779, U.S. Patent 5,447,860, Jones et al., *Nat. Rev. Mol. Cell Biol.*, 2(4), 257-67 (2001), and references cited therein), and in having a structure that includes a N-terminal coiled-coil domain and C-terminal fibrinogen-like domain. The angiopoietins are further functionally characterized by their ability to modulate angiogenesis and related biological activities in the endothelium. Valenzuela et al., *Proc. Natl. Acad. Sci. USA*, 96(5), 1904-1909 (1999). For example, angiopoietin-1 (Ang-1) has been linked to embryonic vascular stabilization, branching morphogenesis, and post-natal angiogenesis. However, not all angiopoietins induce angiogenesis. For example, angiopoietin-2 (Ang-2) acts as an antagonist for Ang-1, disrupting angiogenesis *in vivo*. Maisonpierre et al., *Science*, 277, 55-60 (1997).

[0003] Several factors structurally and/or functionally related to the angiopoietins also have been identified. For example, U.S. Patents 5,972,338, 6,030,831, and 6,057,435 describe a number of protein factors homologous to the angiopoietins. These factors exhibit significant levels of amino acid sequence identity to Ang-1 and/or other angiopoietins and typically contain a fibrinogen-like domain, coiled-coil domain, or both. However, some of these factors may not bind a Tie receptor.

[0004] Fusion proteins containing portions of angiopoietins or angiopoietin homologs are known in the art. Most of these fusion proteins are limited to a protein comprising a single angiopoietin or angiopoietin homolog peptide portion and a heterologous portion typically added to promote protein stability, targeting, or purification. For example, U.S. Patent 6,074,873 discloses fusion proteins comprising an angiopoietin homolog portion where either the N-terminal region of the angiopoietin amino acid sequence is fused to a peptide portion that promotes secretion or the C-terminal portion of the angiopoietin amino acid sequence is fused to an immunogenic polypeptide. International Patent Application WO 00/37642 discloses fusion proteins comprising an angiopoietin peptide portion and a heterologous multimerizing portion derived from an immunoglobulin. International Patent

Application WO 00/75329 discloses fusion proteins comprising an angiogenic factor linked to a molecule that specifically binds the vascular endothelium.

[0005] International Patent Application WO 98/05779 discloses fusion proteins comprising two peptide portions derived from different angiopoietins. However, the fusion proteins of the '779 application are limited to generalized combinations of Ang-1, Ang-2, angiopoietin-3 (Ang-3), and angiopoietin-4 (Ang-4) peptide portions. Similarly, International Patent Applications WO 00/64946 and WO 01/03735 describe particular Ang-1/Ang-2 fusion proteins. International Patent Application WO 01/47951 describes angiopoietin homologs having at least two fibrinogen-like domains or coiled-coil domains. Thus, the fusion proteins of the '779, '946, '735, and '951 applications are limited in their characteristics.

[0006] There remains a need for novel angiopoietin-related factors that exhibit different biological properties than the angiopoietins, angiopoietin homologs, and angiopoietin fusion proteins previously known in the art. The present invention provides such angiopoietin-related factors, as well as polynucleotides encoding such angiopoietin-related factors, vectors comprising such polynucleotides and methods of producing and using such factors, polynucleotides, and vectors. These and other advantages of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

#### BRIEF SUMMARY OF THE INVENTION

[0007] The invention provides a fusion protein comprising (a) a fibrinogen-like domain that exhibits at least about 75% amino acid sequence identity to the fibrinogen-like domain of a first wild-type protein, which binds a receptor that, when activated, promotes or inhibits angiogenesis, and (b) a coiled-coil domain that exhibits at least about 75% amino acid sequence identity to the coiled-coil domain of a second wild-type protein, which increases the affinity of the fusion protein for the receptor, promotes formation of a multimer comprising the fusion protein, or both, wherein the first protein and second protein are different, the first protein and second protein exhibit at least about 30% overall amino acid sequence identity with Ang-1, and the first protein, the second protein, or both proteins, are not Ang-1, Ang-2, Ang-3, or Ang-4.

[0008] The invention further provides a fusion protein comprising (a) a fibrinogen-like domain that exhibits at least about 30% amino acid sequence identity to the fibrinogen-like domain of Ang-1, and (b) a coiled-coil domain that comprises (1) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the coiled-coil domain of zapo1, murine FDRG, or both, (2) an amino acid sequence that exhibits at least about 50% amino acid sequence identity to the coiled-coil domain of NL1, NL5, or both, (3) an amino

acid sequence that exhibits at least about 40% amino acid sequence identity to the coiled-coiled domain of NL8, (4) an amino acid sequence that exhibits at least about 25% amino acid sequence identity to the coiled-coiled domain of FLS 139, or (5) an amino acid sequence that fulfills any combination of (1)-(4), wherein *in vivo* administration or production of the fusion protein promotes or inhibits angiogenesis in a mammalian host.

[0009] The invention also provides a fusion protein comprising (a) a fibrinogen-like domain that comprises (1) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the fibrinogen-like domain of NL1, NL5, NL8, or any combination thereof, (2) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the fibrinogen-like domain of NL4, (3) an amino acid sequence that exhibits at least about 40% amino acid sequence identity to the fibrinogen-like domain of zapo1, murine FDRG, or both, (4) an amino acid sequence that exhibits at least about 45% amino acid sequence identity to the fibrinogen-like domain of NL3, (5) an amino acid sequence that exhibits at least about 30% amino acid sequence identity to the fibrinogen-like domain of FLS 139, or (6) an amino acid sequence which fulfills any combination of (1)-(5), and (b) a coiled-coil domain that exhibits at least about 35% amino acid sequence identity to the coiled-coil domain of Ang-1, Ang-2, Ang-2X, Ang-3, Ang-4, or any combination thereof.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1 is a Kyte & Doolittle hydropathy profile of a first exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0011] Figure 2 is a Kyte & Doolittle hydropathy profile of a second exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0012] Figure 3 is a Kyte & Doolittle hydropathy profile of a third exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0013] Figure 4 is a Kyte & Doolittle hydropathy profile of a fourth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0014] Figure 5 is a Kyte & Doolittle hydropathy profile of a fifth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0015] Figure 6 is a Kyte & Doolittle hydropathy profile of a sixth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0016] Figure 7 is a Kyte & Doolittle hydropathy profile of a seventh exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0017] Figure 8 is a Kyte & Doolittle hydropathy profile of an eighth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0018] Figure 9 is a Kyte & Doolittle hydropathy profile of a ninth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.



[0019] Figure 10 is a Kyte & Doolittle hydropathy profile of a tenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0020] Figure 11 is a Kyte & Doolittle hydropathy profile of an eleventh exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0021] Figure 12 is a Kyte & Doolittle hydropathy profile of a twelfth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0022] Figure 13 is a Kyte & Doolittle hydropathy profile of a thirteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0023] Figure 14 is a Kyte & Doolittle hydropathy profile of a fourteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0024] Figure 15 is a Kyte & Doolittle hydropathy profile of a fifteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0025] Figure 16 is a Kyte & Doolittle hydropathy profile of a sixteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0026] Figure 17 is a Kyte & Doolittle hydropathy profile of a seventeenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0027] Figure 18 is a Kyte & Doolittle hydropathy profile of an eighteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

[0028] Figure 19 is a Kyte & Doolittle hydropathy profile of a nineteenth exemplary coiled-coil domain suitable for incorporation in a fusion protein of the invention.

#### DETAILED DESCRIPTION OF THE INVENTION

[0029] The invention provides novel angiopoietin-related factors, particularly novel fusion proteins, the novel ARF homolog Ang-2X, and synthetic homologs of known ARFs. The invention further provides polynucleotides encoding such ARFs, vectors comprising such polynucleotides, and methods of producing such fusion proteins, polynucleotides, and vectors. The invention additionally provides methods of using such novel ARFs, and new methods of using ARFs already known in the art.

[0030] An "angiopoietin related factor" (ARF) is any protein of at least about 100 amino acid residues, preferably at least about 200 amino acid residues, more preferably at least about 300 amino acid residues, and typically about 350-600 amino acid residues (most typically about 500 amino acid residues) that exhibits at least about 20% overall amino acid sequence identity, preferably at least about 25% amino acid sequence identity, and even more preferably at least about 30% amino acid sequence identity (e.g., at least about 35%, at least about 40%, or even at least about 50% amino acid sequence identity) to angiopoietin-1 (SEQ ID NO:1).

[0031] The fusion proteins of the invention comprise at least two peptide portions, each of which independently and separately (1) share an identical amino acid sequence with a naturally occurring ARF peptide portion, (2) comprise an amino acid sequence that exhibits a significant amount of sequence identity (at least about 25% amino acid sequence identity, preferably at least about 30% amino acid sequence identity) to the amino acid sequence of a wild-type ARF peptide portion, (3) comprise an amino acid sequence that exhibits a significant amount of sequence homology (at least about 30% sequence homology, preferably at least about 35% sequence homology) to a wild-type ARF peptide portion, (4) comprise an amino acid sequence that exhibits significant weight homology to and/or similar hydropathy profile with a wild-type ARF peptide portion, (5) are encoded by a polynucleotide that hybridizes, under at least moderate stringency conditions with the complement of a polynucleotide that, when transcribed and translated, produces (or otherwise results in the production of, e.g., after post-translational modification) a protein that is identical to a wild-type ARF peptide portion, or would so hybridize but for the degeneracy of the genetic code, (6) are bound by antibodies to a naturally occurring ARF peptide portion, or (7) exhibit any combination of characteristics (1)-(6). ARF fusion protein peptide portions that exhibit more than one of the six characteristics are preferred, and ARF fusion protein peptide portions that exhibit all of characteristics (4)-(6) and at least one of characteristics (1)-(3) (most preferably characteristic (1)) are particularly preferred.

[0032] A "peptide portion" is any amino acid sequence contained within a larger peptide, polypeptide, or protein (which terms are used synonymously herein, unless otherwise indicated) of at least about 15, preferably at least about 20, more preferably at least about 25, and even more preferably at least about 30 amino acid residues (e.g., at least about 40, at least about 50, at least about 70, at least about 100, or even more amino acid residues).

[0033] "Identity" (sometimes referred to as "overall" identity) with respect to amino acid or polynucleotide sequences refers to the percentage of residues or bases that are identical in the two sequences when the sequences are optimally aligned. If, in the optimal alignment, a position in a first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, the sequences exhibit identity with respect to that position. The level of identity between two sequences (or "percent sequence identity") is measured as a ratio of the number of identical positions shared by the sequences with respect to the size of the sequences (i.e., percent sequence identity = (number of identical positions/total number of positions) x 100).

[0034] The "optimal alignment" is the alignment that provides the highest identity between the aligned sequences. In obtaining the optimal alignment, gaps can be introduced, and some amount of non-identical sequences and/or ambiguous sequences can be ignored.

Preferably, if a gap needs to be inserted into a first sequence to achieve the optimal alignment, the percent identity is calculated using only the residues that are paired with a corresponding amino acid residue (i.e., the calculation does not consider residues in the second sequences that are in the "gap" of the first sequence). However, it is often preferable that the introduction of gaps and/or the ignoring of non-homologous/ambiguous sequences are associated with a "gap penalty."

[0035] A number of mathematical algorithms for rapidly obtaining the optimal alignment and calculating identity between two or more sequences are known and incorporated into a number of available software programs. Examples of such programs include the MATCH-BOX, MULTAIN, GCG, FASTA, and ROBUST programs for amino acid sequence analysis, and the SIM, GAP, NAP, LAP2, GAP2, and PIPMAKER programs for nucleotide sequences. Preferred software analysis programs for both amino acid and polynucleotide sequence analysis include the ALIGN, CLUSTAL W (e.g., version 1.6 and later versions thereof), and BLAST programs (e.g., BLAST 2.1, BL2SEQ, and later versions thereof).

[0036] For amino acid sequence analysis, a weight matrix, such as the BLOSUM matrixes (e.g., the BLOSUM45, BLOSUM50, BLOSUM62, and BLOSUM80 matrixes), Gonnet matrixes (e.g., the Gonnet40, Gonnet80, Gonnet120, Gonnet160, Gonnet250, and Gonnet350 matrixes), or PAM matrixes (e.g., the PAM30, PAM70, PAM120, PAM160, PAM250, and PAM350 matrixes), are used in determining identity. BLOSUM matrixes are preferred. The BLOSUM50 and BLOSUM62 matrixes are typically most preferred. In the absence of availability of such weight matrixes (e.g., in nucleic acid sequence analysis and with some amino acid analysis programs), a scoring pattern for residue/nucleotide matches and mismatches can be used (e.g., a +5 for a match and -4 for a mismatch pattern).

[0037] The ALIGN program produces an optimal global alignment of the two chosen protein or nucleic acid sequences using a modification of the dynamic programming algorithm described by Myers and Miller, *CABIOS*, 4, 11-17 (1988). Preferably, if available, the ALIGN program is used with weighted end-gaps. If gap opening and gap extension penalties are available, they are preferably set between about -5 to -15 and 0 to -3, respectively, more preferably about -12 and -0.5 to -2, respectively, for amino acid sequence alignments, and -10 to -20 and -3 to -5, respectively, more preferably about -16 and -4, respectively, for nucleic acid sequence alignments. The ALIGN program and principles underlying it are further described in, e.g., Pearson et al., *Proc. Natl. Acad. Sci. USA*, 85, 2444-48 (1988), and Pearson et al., *Methods Enzymol.*, 183, 63-98 (1990).

[0038] The BLAST programs provide analysis of at least two amino acid or nucleotide sequences, either by aligning a selected sequence against multiple sequences in a database (e.g., GenSeq), or, with BL2SEQ, between two selected sequences. BLAST programs are

preferably modified by low complexity filtering programs such as the DUST or SEG programs, which are preferably integrated into the BLAST program operations (see, e.g., Wootton et al., *Compu. Chem.*, 17, 149-63 (1993), Altschul et al., *Nat. Genet.*, 6, 119-29 (1994), Hancock et al., *Comput. Appl. Biosci.*, 10, 67-70 (1994), and Wootton et al., *Meth. in Enzym.*, 266, 554-71 (1996)). If a lambda ratio is used, preferred settings for the ratio are between 0.75 and 0.95, more preferably between 0.8 and 0.9. If gap existence costs (or gap scores) are used, the gap existence cost preferably is set between about -5 and -15, more preferably about -10, and the per residue gap cost preferably is set between about 0 to -5, more preferably between 0 and -3 (e.g., -0.5). Similar gap parameters can be used with other programs as appropriate. The BLAST programs and principles underlying them are further described in, e.g., Altschul et al., *J. Mol. Biol.*, 215, 403-10 (1990), Karlin and Altschul, *Proc. Natl. Acad. Sci. USA*, 87, 2264-68 (1990) (as modified by Karlin and Altschul, *Proc. Natl. Acad. Sci. USA*, 90, 5873-77 (1993)), and Altschul et al., *Nucl. Acids Res.*, 25, 3389-3402 (1997).

[0039] For multiple sequence analysis, the CULSTAL W program can be used. The CLUSTAL W program desirably is run using "dynamic" (versus "fast") settings. Preferably, nucleotide sequences are compared using the BESTFIT matrix, whereas amino acid sequences are evaluated using a variable set of BLOSUM matrixes depending on the level of identity between the sequences (e.g., as used by the CLUSTAL W version 1.6 program available through the San Diego Supercomputer Center (SDSC)). Preferably, the CLUSTAL W settings are set to the SDSC CLUSTAL W default settings (e.g., with respect to special hydrophilic gap penalties in amino acid sequence analysis). The CLUSTAL W program and underlying principles of operation are further described in, e.g., Higgins et al., *CABIOS*, 8(2), 189-91 (1992), Thompson et al., *Nucleic Acids Res.*, 22, 4673-80 (1994), and Jeanmougin et al., *Trends Biochem. Sci.*, 23, 403-07 (1998).

[0040] Several commercially available software suites incorporate the ALIGN, BLAST, and CLUSTAL W programs and similar functions, and may include significant improvements in settings and analysis. Examples of such programs include the GCG suite of programs and those available through DNASTAR, Inc. (Madison, Wisconsin). Particular preferred programs include the Lasergene and Protean programs sold by DNASTAR.

[0041] Because various algorithms, matrixes, and programs are commonly used to analyze sequences, amino acid and polynucleotide sequences are preferably characterized in terms of approximate identities by indicating a range of identity "about" a particular identity (e.g., +/- 10%, more preferably +/- 8%, and even more preferably +/- 5% of the particular identity). Alternatively, an exact identity can be measured by using only one of the aforementioned programs, preferably one of the BLAST programs, as described herein. An amino acid sequence of a fusion protein peptide portion can alternatively exhibit

significant (at least about 30%, preferably at least about 35%) sequence “homology” to a wild-type ARF peptide portion, while failing to exhibit a significant level of amino acid sequence identity. Homology is a function of the number of corresponding conserved and identical amino acid residues in the optimal homology alignment. The “optimal homology alignment” is the alignment that provides the highest level of homology between two amino acid sequences, using the principles described above with respect to the “optimal alignment.” Conservative amino acid residue substitutions involve exchanging a member within one class of amino acid residues for a residue that belongs to the same class. Fusion protein peptide portions containing conservative substitutions are expected to substantially retain the biological properties and functions associated with their wild-type counterpart or wild-type counterpart portions. The classes of amino acids and the members of those classes are presented in Table 1.

*Table 1 – Amino Acid Residue Classes*

Amino Acid Class	Amino Acid Residues
Acidic Residues	ASP and GLU
Basic Residues	LYS, ARG, and HIS
Hydrophilic Uncharged Residues	SER, THR, ASN, and GLN
Aliphatic Uncharged Residues	GLY, ALA, VAL, LEU, and ILE
Non-polar Uncharged Residues	CYS, MET, and PRO
Aromatic Residues	PHE, TYR, and TRP

[0042] The fusion protein peptide portion preferably will exhibit high weight homology to a naturally occurring ARF peptide portion. “High weight homology” means that at least about 40%, preferably at least about 60%, and more preferably at least about 70% of the non-identical amino acid residues are members of the same weight-based “weak conservation group” or “strong conservation group” as the corresponding amino acid residue in the wild-type ARF peptide portion. Strong group conservation is preferred. Weight-based conservation is determined on the basis of whether the non-identical corresponding amino acid is associated with a positive score on one of the weight-based matrices described herein (e.g., the BLOSUM50 matrix and preferably the PAM250 matrix). Weight-based strong conservation groups include Ser Thr Ala, Asn Glu Gln Lys, Asn His Gln Lys, Asn Asp Glu Gln, Gln His Arg Lys, Met Ile Leu Val, Met Ile Leu Phe, His Tyr, and Phe Tyr Trp. Weight-based weak conservation groups include Cys Ser Ala, Ala Thr Val, Ser Ala Gly, Ser Thr Asn Lys, Ser Thr Pro Ala, Ser Gly Asn Asp, Ser Asn Asp Glu Gln Lys, Asn Asp Glu Gln His Lys, Asn Glu Gln His Arg Lys, Phe Val Leu Ile Met, and His Phe Tyr. The CLUSTAL W sequence analysis program provides analysis of

weight-based strong conservation and weak conservation groups in its output, and offers the preferred technique for determining weight-based conservation, preferably using the CLUSTAL W default settings used by SDSC.

[0043] Additionally, the fusion protein peptide portion can be a peptide portion that exhibits a similar hydropathy profile (hydrophilicity) to a wild-type ARF protein peptide portion. A hydropathy profile can be determined using the Kyte & Doolittle index, the scores for each naturally occurring amino acid in the index being as follows: I (+4.5), V (+4.2), L (+3.8), F (+2.8), C (+2.5), M (+1.9); A (+1.8), G (-0.4), T (-0.7), S (-0.8), W (-0.9), Y (-1.3), P (-1.6), H (-3.2); E (-3.5), Q (-3.5), D (-3.5), N (-3.5), K (-3.9), and R (-4.5) (see, e.g., U.S. Patent 4,554,101 and Kyte & Doolittle, *J. Molec. Biol.*, 157, 105-32 (1982) for further discussion). Preferably, at least about 45%, preferably at least about 60%, and more preferably at least about 75% (e.g., at least about 85%, at least about 90%, or at least about 95%) of the amino acid residues which differ from the naturally occurring ARF peptide portions exhibit less than a  $\pm 2$  change in hydrophilicity, more preferably less than a  $\pm 1$  change in hydrophilicity, and even more preferably less than a  $\pm 0.5$  change in hydrophilicity. Overall, the fusion protein peptide portions of the invention preferably exhibit a total change in hydrophilicity of less than about 150, more preferably less than about 100, and even more preferably less than about 50 (e.g., less than about 30, less than about 20, or less than about 10) from their wild-type counterparts. Examples of typical amino acid substitutions that retain similar or identical hydrophilicity include arginine-lysine substitutions, glutamate-aspartate substitutions, serine-threonine substitutions, glutamine-asparagine substitutions, and valine-leucine-isoleucine substitutions. The GREASE program, available through the SDSC, provides a convenient way for quickly assessing the hydropathy profile of a peptide portion. For example, a coiled-coil domain fusion protein peptide portion will desirably exhibit a predominately negative hydropathy profile (i.e., at least 50% of the GREASE program line output is less than 0, representing that at least 50% of the amino acid residues exhibit a Kyte-Doolittle index score of less than 0). The fusion protein coiled-coil domain will typically exhibit a hydropathy profile where all residues exhibit a hydropathy score equal or less than leucine and more preferably equal or less than alanine. Desirably, a majority of the residues in the coiled-coil domain will exhibit a hydropathy profile equal to or less than glycine. Typically and preferably, the coiled-coil domain will be substantially formed (e.g., at least about 70%, preferably at least about 80%, and more preferably at least about 90%) of residues having a Kyte & Doolittle score of between -4 and 2, and more preferably between -3 and 1. Desirably, all amino acid residues in the coiled-coil domain will have a score between -3 and 1. A fusion protein coiled-coil domain will preferably exhibit a GREASE program graphical line output comprising a pattern of several (typically about 10-15) peaks and valleys of residues scoring

between -3 to -2 and 0 to +1 respectively. GREASE program outputs of select examples of preferred coiled-coil domains are provided in Figs. 1-19. The fusion protein preferably comprises a coiled-coil domain having a hydropathy profile substantially identical (e.g., less than about a 10% difference from) or identical to one of the profiles shown in either Figs. 1-3 or 4-9.

**[0044]** In yet another alternative, the fusion protein peptide portion can comprise or consist of a peptide of at least about 40 amino acid residues, preferably at least about 75 amino acid residues, and more preferably at least about 150 (e.g., at least about 200, at least about 250, or more) amino acid residues encoded by a polynucleotide that hybridizes to (1) the complement of a polynucleotide that, when expressed, results in a naturally occurring ARF peptide portion, under at least moderate, preferably high, stringency conditions, or (2) a polynucleotide which would hybridize to the complement of such a sequence under such conditions but for the degeneracy of the genetic code. Alternatively, the peptide portion can comprise a sequence encoded by a polynucleotide that selectively hybridizes to a wild-type ARF peptide portion-encoding polynucleotide of at least about 60 nucleotides (preferably at least about 120 nucleotides, and more preferably at least about 150 nucleotides, or more) with respect to other wild-type ARF-encoding polynucleotide sequences, and, more preferably selectively with respect to other wild-type proteins of the same organism, species, family, and/or kingdom.

**[0045]** Exemplary moderate stringency conditions include overnight incubation at 37°C in a solution comprising 20% formamide, 5x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 mg/mL denatured sheared salmon sperm DNA, followed by washing the filters in 1x SSC at about 37-50°C, or substantially similar conditions, e.g., the moderately stringent conditions described in Sambrook et al., *MOLECULAR CLONING: A LABORATORY MANUAL* (Cold Spring Harbor Press 1989). High stringency conditions are conditions that use, for example, (1) low ionic strength and high temperature for washing, such as 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate (SDS) at 50°C, (2) employ a denaturing agent during hybridization, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin (BSA)/0.1% Ficoll/0.1% polyvinylpyrrolidone (PVP)/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C, or (3) employ 50% formamide, 5x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at (i) 42°C in 0.2x SSC, (ii) at 55°C in 50% formamide and (iii) at 55°C in 0.1x SSC (preferably in combination with EDTA). Additional details and

explanation of stringency of hybridization reactions are provided in, e.g., Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Wiley Interscience Publishers 1995).

[0046] Another possibility is that the fusion protein peptide portion comprises or consists of an amino acid sequence that is bound by an antibody that also binds a wild-type ARF peptide portion. For example, the fusion protein peptide portion can be a peptide portion that is bound by the wild-type ARF antibodies described in, e.g., U.S. Patent 6,166,185, and/or International Patent Applications WO 00/18804, WO 00/18437, and WO 99/15653. Antibodies to Ang-1, Ang-2, Ang-3, and Ang-4 are commercially available through Research Diagnostics, Inc. (Flanders NJ). Other suitable wild-type ARF antibodies are described in the various patent documents and references directed to ARFs discussed elsewhere herein.

[0047] The production of new antibodies to the wild-type ARFs, and to the novel ARFs of the invention, also can be facilitated using any suitable technique known in the art. Examples of suitable techniques for obtaining such antibodies are provided in, e.g., Gavilodono et al., *Biotechniques*, 29(1), 128-32, 134-6, and 138 (passim) (2000), Nelson et al., *Mol. Pathol.*, 53(3), 111-7 (2000), Laurino et al., *Ann. Clin. Lab. Sci.*, 29(3), 158-66 (1999), Rapley, *Mol. Biotechnol.*, 3(2), 139-54 (1995), Zaccolo et al., *Int. J. Clin. Lab. Res.*, 23(4), 192-8 (1993), Morrison, *Annu. Rev. Immunol.*, 10, 239-65 (1992), "Antibodies, Antigens, and Molecular Mimicry," *Meth. Enzymol.*, 178 (John J. Langone, Ed., Academic Press, November 1989), Moore, *Clin. Chem.*, 35(9), 1849-53 (1989), Rosalki et al., *Clin. Chim. Acta*, 183(1), 45-58 (1989), and Tami et al., *Am. J. Hosp. Pharm.*, 43(11), 2816-25 (1986), as well as U.S. Patents 4,022,878, 4,350,683, and 4,022,878. A preferred technique for producing antibodies is provided in Border et al., *Proc. Natl. Acad. Sci., USA*, 97(20), 10701-05 (2000).

[0048] The fusion protein peptide portion alternatively, or, typically and preferably, additionally, can comprise or consist of a peptide portion that exhibits structural similarity to a wild-type ARF peptide portion. It is further desired that the fusion protein exhibits overall structural similarity to a wild-type ARF. Structural similarity can be determined by any suitable technique, preferably using a suitable software program for making such assessments. Examples of such programs include the MAPS program and the TOP program (described in Lu, *Protein Data Bank Quarterly Newsletter*, #78, 10-11 (1996), and Lu, *J. Appl. Cryst.*, 33, 176-183 (2000)). The fusion protein peptide portion, and preferably the fusion protein overall, will desirably exhibit a low structural diversity, topological diversity (e.g., a topological diversity of less than about 20, preferably less than about 15, and more preferably less than about 10), or both, with respect to a wild-type ARF counterpart. Alternatively, the structure of the fusion protein or fusion protein peptide portion can be compared to the desired ARF or ARF peptide portion using the PROCHECK program



(described in, e.g., Laskowski, *J. Appl. Cryst.*, 26, 283-291 (1993)), the MODELLER program, or commercially available programs incorporating such features. Alternatively, a sequence comparison using a program such as the PredictProtein server (available at <http://dodo.cpmc.columbia.edu/predictprotein/>) can reveal similar structure for the fusion protein or fusion protein peptide portion and a wild-type ARF peptide portion counterpart. Additional techniques for analyzing protein structure that can be applied to determine structural similarity are described in, e.g., Yang and Honig, *J. Mol. Biol.*, 301(3), 665-78 (2000), Aronson et al., *Protein Sci.*, 3(10), 1706-11 (1994), Marti-Remon et al., *Annu. Rev. Biophys. Biomol. Struct.*, 29, 291-325 (2000), Halaby et al., *Protein Eng.*, 12(7), 563-71 (1999), Basham, *Science*, 283, 1132 (1999), Johnston et al., *Crit. Rev. Biochem. Mol. Biol.*, 29(1), 1-68 (1994), Moult, *Curr. Opin. Biotechnol.*, 10(6), 583-6 (1999), Benner et al., *Science*, 274, 1448-49 (1996), and Benner et al., *Science*, 273, 426-8 (1996).

**[0049]** The fusion protein of the invention desirably has an overall structural conformation such that the overall structure of the fusion protein does not interfere with the function of the individual ARF peptide portions. In addition to the techniques described above, conformation of the peptide portions can be assessed using conformation-dependent antibodies. If necessary, linker sequences, such as the linker sequences described further herein, can be used to separate peptide portions in order to avoid steric hindrance and/or undesired interactions at the tertiary or quaternary levels of structure. The fusion protein will advantageously be designed such that multimerization of a heterologous peptide portion, e.g., a VEGF peptide portion, is not interfered with by the multimerization of a second peptide portion, e.g., the multimerization domain of an ARF, such as the Ang-1 CCD. The fusion protein also will desirably be designed such that post-translational modification of the fusion protein is of a manner suitable for retaining the function of the peptide portions, typically by expression of the fusion protein with appropriate signal sequences, examples of which are discussed further herein.

**[0050]** The fusion protein can include any combination of peptide portions having any of the aforementioned qualities. Thus, for example, the fusion protein can include a first peptide portion comprising an amino acid sequence identical to the amino acid sequence of a first wild-type ARF peptide portion and a second peptide portion comprising a sequence exhibiting 100% sequence homology, but less than 100% sequence identity, but to a second ARF peptide portion. The fusion protein can include any suitable number of ARF peptide portions (peptide portions exhibiting one of the aforementioned seven qualities, preferably exhibiting significant sequence identity or sequence homology to a wild-type ARF peptide portion). For example, the fusion protein can include 3, 4, 5, or even more ARF peptide portions. Where the fusion protein comprises three or more ARF peptide portions, more

than one of the peptide portions can be identical, homologous, and/or otherwise similar to the same wild-type ARF peptide portion.

[0051] Where the fusion protein comprises only two ARF peptide portions each ARF peptide portion will desirably exhibit higher sequence identity and/or homology to a different wild-type ARF than the other ARF peptide portion. Preferably, at least one of the ARF fusion protein peptide portions in such a fusion protein will not be an angiopoietin and, more preferably, is not selected from Ang-1, Ang-2, Ang-3, and Ang-4.

[0052] The fusion protein exhibits less than 100% overall sequence identity to a wild-type ARF. For example, the fusion protein can exhibit about 95% or less, about 90% or less, about 80% or less, about 70% or less, about 60% or less, or even about 50% or less overall amino acid sequence identity to any wild-type ARF. The fusion protein also can lack any peptide portions that exhibit 100% local sequence identity to a wild-type ARF. For example, the fusion protein can lack any peptide portions that exhibit about 90% or more, about 80% or more, about 70% or more, or even about 60% or more local sequence identity to a wild-type ARF.

[0053] Local sequence identity can be determined using local sequence alignment software, e.g., the BLAST programs described above, the LFASTA program, or, more preferably, the LALIGN program. Preferably, the LALIGN program using a BLOSUM50 matrix analysis used for amino acid sequence analysis, and a +5 match/-4 mismatch analysis used for polynucleotide sequence analysis. Gap extension and opening penalties are preferably the same as those described above with respect to analysis with the ALIGN program. For LALIGN (or other program) analysis using k-tup value settings (also referred to as "k-tuple" or ktup values), a k-tup value of 0-3 for proteins, and 0-10 (e.g., about 6) for nucleotide sequences, is preferred.

[0054] The fusion protein will comprise a fibrinogen-like domain (FLD), a coiled-coil domain (CCD), or, typically and preferably, a FLD and a CCD. Desirably, the fusion protein fibrinogen-like domain exhibits at least about 25% amino acid sequence identity, preferably at least about 30% amino acid sequence identity, and more preferably at least about 35% amino acid sequence identity to the Ang-1 fibrinogen-like domain (SEQ ID NO: 2) and/or the KIA0003 associated protein (GenBank Accession No. NP 001137) (SEQ ID NO: 3) (hereinafter referred to as KAP). The fusion protein coiled-coil domain desirably will exhibit at least about 10% amino acid sequence identity, preferably at least about 15% amino acid sequence identity, more preferably at least about 20% amino acid sequence identity, and even more preferably at least about 30% amino acid sequence identity to the CCD of Ang-1 (SEQ ID NO: 4). Desirably, the fusion protein FLD, CCD, or both domains will exhibit a higher level of local sequence identity to a non-angiopoietin ARF than to angiopoietin ARFs, and more particularly exhibits a higher level of local sequence identity

to an ARF other than Ang-1, Ang-2, Ang-3, or Ang-4. While the fusion protein can comprise any suitable number of CCDs and FLDs (e.g., 2, 3, or more CCDs and/or FLDs), it will preferably comprise a single FLD and CCD.

**[0055]** A “fibrinogen-like domain” (FLD) is a peptide domain of at least about 75, more preferably at least about 150, and even more preferably at least about 210 (e.g., about 175-250, typically about 210-230) amino acid residues in length, that exhibits at least about 25%, preferably at least about 35%, and more preferably at least about 40% amino acid sequence identity to (e.g., 20-70% identity) or at least such levels of local sequence identity to the alpha, beta, or gamma chains (typically to the C-terminal globular domain thereof) of a naturally occurring mammalian fibrinogen (e.g., human fibrinogen alpha (1<sup>st</sup> example (SEQ ID NO: 4) and 2<sup>nd</sup> example (SEQ ID NO: 5)), human fibrinogen beta (1<sup>st</sup> example (SEQ ID NO: 6) and 2<sup>nd</sup> example (SEQ ID NO: 7)), and/or human fibrinogen gamma (1<sup>st</sup> example (SEQ ID NO: 8) and 2<sup>nd</sup> example (SEQ ID NO: 9))). As indicated above, the fusion protein FLD also desirably exhibits at least about 25% amino acid sequence identity to the Ang-1 FLD and/or KAP.

**[0056]** FLDs can be identified using any suitable technique, such as by applying any of the sequence alignment algorithms or programs discussed elsewhere herein to the subject sequence and the chain of a wild-type fibrinogen. Preferably, the subject fusion protein (or other ARF) will comprise an amino acid sequence, which, when submitted to Conserved Domain Database (CDD) analysis (e.g., by submission to the NCBI BLAST program with the CDD (sometimes indicated as CD) analysis option selected), will result in the program identifying the presence of a conserved “FBG” (fibrinogen related domain - CD=smart00186) and/or “Fibrinogen-C” domain (CD=pfam00147), or, most desirably, both types of domains, in the subject amino acid sequence.

**[0057]** The fusion protein FLD desirably will comprise at least two cysteine residues, preferably at least four cysteine residues, more preferably at least five cysteine residues, and even more preferably at least six cysteine residues, which desirably form internal disulfide bonds. Preferably, at least two, and more preferably at least four, of the FLD’s cysteine residues are positioned in the C-terminal half of the FLD.

**[0058]** A “coiled-coil domain” (CCD) is a peptide domain comprising at least one alpha helix domain, wherein one side of the alpha helix domain comprises a predominantly hydrophobic portion (i.e., at least about 50% of the amino acid residues on a side of the alpha helix are hydrophobic, typically at least about 65% of the amino acid residues on a side of the alpha helix are hydrophobic (hydrophobic amino acid residues are listed in Table 1, *supra*)). The CCD can include any suitable number of alpha helix domains. Typically, the CCD will include 1-10 alpha helices (more typically 1-5), each of which are usually about 10 amino acid residues in length. The alpha helices can be antiparallel or parallel in

orientation. The alpha helix domain is well known in the art and, as such, is only briefly discussed here. Further description of the features associated with the alpha helix domain can be found in, e.g., Stryer, *BIOCHEMISTRY*, W.H. Freeman & Co. (New York), 3d Edition (1988), Scholtz et al., *Annu. Rev. Biophys. Biomol. Struct.*, 21, 95-118 (1992), Sugeta et al., *Biopolymers*, 5, 673 - 679 (1967), and references cited therein. Analytical techniques, and computer programs incorporating such techniques for identifying alpha helices, also are known in the art. See, e.g., Kumar et al., *Biophys. J.*, 71, 1574-1586 (1996), Kumar et al., *Biophys. J.*, 75, 1935-44 (1998), and Bansal et al., *J. Biomolec. Struct. Dynamics*, 17, 811-19 (2000). Examples of suitable programs for identifying alpha helices using an amino acid sequence include the GOR4 program, which uses the algorithm of Garnier et al., *Meth. Enzym.*, 266, 97-120 (1996), the CHOFAS program, which uses the algorithms of Chou et al., *Adv. Enzymol.*, 47, 45-148 (1978), and Pearson et al., *Proc. Natl. Acad. Sci. USA*, 85, 2444-48 (1988), and the PELE program which combines multiple algorithms. All of these programs are accessible through the San Diego Supercomputer Center (SDSC).

**[0059]** Typically and preferably, the coiled-coil domain will include at least one sequence of the heptad pattern  $h_a-x_b-x_c-h_d-x_e-x_f-x_g$ , where "h" represents a hydrophobic amino acid residue, "x" represents any amino acid residue, and subscripted letters reference positions in the sequence. Typically, the amino acid residues at positions  $x_e$  and  $x_g$  will be polar residues. Often the CCD will include multiple heptad repeats of this pattern. The hydrophobic heptad repeat usually imparts greater stability to the CCD than over an otherwise identical multiple alpha helix domain, by adopting the Crick "knobs-into-holes" packing configuration, where the  $h_a$  and  $h_d$  hydrophobic residues interact with the internal (i.e., central) portions of a neighboring alpha helix (typically an alpha helix positioned in the CCD, but interactions with a peptide portion of a different polypeptide also are possible, particularly when the CCD is involved with forming multimers, which are further discussed below).

**[0060]** CCDs can be identified by any suitable technique. Conveniently, CCDs can usually be identified through direct amino acid sequence analysis. Several analytical techniques for identifying CCDs and computer programs incorporating these techniques are available. Any suitable sequence analysis technique or program can be used. Examples of suitable programs include the COILS program (available at [http://www.ch.embnet.org/software/COILS\\_form.html](http://www.ch.embnet.org/software/COILS_form.html)) and the PARCOILS program (available at <http://nightingale.lcs.mit.edu/cgi-bin/score>). Other suitable programs include the PEP-COIL program, the COILSCAN program, and the coil analysis subprograms of commercially available sequence analysis software (e.g., the GCG program suite, or the PROTEAN program available through DNA Star Inc. (Madison, WI)). Alternatively, other protein structure techniques can be used to identify the presence of a CCD, such as X-ray

diffraction analysis, crystallographic analysis, or three-dimensional imaging techniques. CCDs and the identification of CCDs are further described in Burkhard et al., *Trends Cell Bio.*, 11, 82-88 (2001), Beck et al., *J. Struct. Biol.*, 122, 17-29 (1998), Lupas, *Curr. Opin. Struct. Biol.*, 7(3), 388-93 (1997), Kammerer, *Matrix Biol.*, 15, 555-68 (1997), Nilges et al., *Proteins*, 15, 133-46 (1993), and Adamson et al., *Curr. Opin. Biotechnol.*, 4(4), 428-37 (1993).

**[0061]** The CCD typically and desirably will comprise an amino acid sequence of at least about 10 amino acid residues (preferably at least about 20 amino acid residues) which exhibit a score of at least about 0.5, more preferably at least about 0.65, and even more preferably at least about 0.75, in the 28 residue window, when the sequence is analyzed by the COILS program. Alternatively, or preferably additionally, the CCD will comprise a sequence of at least about 10 amino acid residues that exhibit a score of at least about 0.3, more preferably at least about 0.4, and even more preferably at least about 0.45 when the sequence is analyzed by the PARCOILS program.

**[0062]** The fusion protein FLD can comprise or consist of a peptide portion that exhibits 100% amino acid sequence identity to a wild-type ARF FLD. The fusion protein FLD can exhibit 100% sequence identity to any suitable ARF FLD. Preferred wild-type FLDs include the Ang-1 FLD, KAP, the Ang-2 FLD (SEQ ID NO: 10), the Ang-3 FLD (SEQ ID NO: 11), the Ang-4 FLD (SEQ ID NO: 12), the NL1 FLD (SEQ ID NO: 13), the NL3 FLD (SEQ ID NO: 14), the NL4 FLD (SEQ ID NO: 15), the NL5 FLD (SEQ ID NO: 16), the NL8 FLD (SEQ ID NO: 17), the FLS 139 FLD (SEQ ID NO: 18), the zapo1 FLD (SEQ ID NO: 19), and the murine FDRG FLD (SEQ ID NO: 20). Particularly preferred wild-type FLDs include the Ang-1 FLD and/or KAP, the NL1 FLD, and the NL5 FLD.

**[0063]** The fusion protein CCD can comprise or consist of a peptide portion that exhibits 100% amino acid sequence identity to a wild-type ARF CCD. The fusion protein CCD can exhibit 100% amino acid sequence identity to any suitable wild-type ARF CCD. Preferred wild-type CCDs include the Ang-1 CCD, the Ang-2 CCD, which is predicted to be sequence 1 (SEQ ID NO: 21), sequence 2 (SEQ ID NO: 22), sequence 3 (SEQ ID NO: 23), or sequence 4 (SEQ ID NO: 24), the Ang-3 CCD (SEQ ID NO: 25), the Ang-4 CCD (SEQ ID NO: 26), the NL1 CCD (SEQ ID NO: 27), the NL2 CCD (SEQ ID NO: 28), the NL4 CCD (SEQ ID NO: 29), the NL5 CCD (SEQ ID NO: 30), the NL8 CCD (SEQ ID NO: 31), the FLS 139 CCD (SEQ ID NO: 32), the zapo1 CCD (SEQ ID NO: 33), and the murine FDRG CCD (SEQ ID NO: 34). Particularly preferred wild-type CCDs include the Ang-1 CCD, the Ang-2 CCD, the NL1 CCD, and the NL5 CCD. Another preferred CCD (described further herein) is the CCD of the novel ARF, Ang-2X (predicted to be amino acid sequence 1 (SEQ ID NO: 35), sequence 2 (SEQ ID NO: 36), or sequence 3 (SEQ ID NO: 37)). The fusion protein also can comprise an Ang-2X FLD (SEQ ID NO: 38).

[0064] The above described wild-type ARF FLDs and CCDs can be combined in any suitable manner in the fusion protein, so long as the FLD and CCD do not exhibit 100% local sequence identity to the same wild-type ARF. In addition, the fusion protein can comprise a FLD or CCD that exhibits 100% identity to a wild-type ARF peptide portion and a FLD or CCD that is homologous to a wild-type ARF peptide portion, but does not exhibit 100% local sequence identity to a wild-type ARF. A "homologous peptide portion" or "homolog" refers to any peptide portion that exhibits any of qualities (2)-(6) described above. Preferably, the homologous ARF peptide portion will exhibit at least about 30% amino acid sequence identity, or at least about 35% amino acid sequence homology, to a wild-type ARF peptide portion.

[0065] A preferred fusion protein comprises a FLD that exhibits 100% amino acid sequence identity to KAP or the Ang-1 FLD and a CCD that exhibits 100% amino acid sequence identity to a wild-type ARF other than Ang-1, Ang-2, Ang-3, or Ang-4. Preferably, the fusion protein comprises a CCD that exhibits 100% amino acid sequence identity to a wild-type ARF that is not an angiopoietin. More preferably, the fusion protein comprises a CCD that exhibits 100% amino acid sequence identity to the NL1 CCD, NL4 CCD, the NL5 CCD, the NL8 CCD, the FLS 139 CCD, the zapo1 CCD, or the murine FDRG CCD. Most preferably, the fusion protein comprises a CCD that exhibits 100% amino acid sequence identity to the NL1 CCD or NL5 CCD.

[0066] Another preferred fusion protein comprises a FLD that exhibits 100% amino acid sequence identity to the FLD of a wild-type ARF other than the Ang-1, Ang-2, Ang-3, or Ang-4 FLD, and more preferably exhibits 100% amino acid sequence identity to a non-angiopoietin ARF FLD. Such a fusion protein desirably further comprises a CCD that exhibits 100% amino acid sequence to a wild-type ARF, most preferably to the CCD of Ang-1 or the CCD of Ang 2X.

[0067] Another preferred fusion protein comprises a FLD or CCD that exhibits 100% amino acid sequence identity to the FLD or CCD of NL1. Preferably, the fusion protein will comprise a non-NL1 CCD or FLD, which will exhibit at least about 45%, more preferably at least about 55%, and optimally about 100% sequence identity to the CCD or FLD of NL5, as applicable.

[0068] In yet another aspect, the invention provides a fusion protein comprising a FLD or CCD that exhibits about 100% amino acid sequence identity to the FLD or CCD of NL5, as applicable. Such fusion proteins desirably comprise a non-NL5 FLD or CCD that exhibits at least about 45%, more preferably at least about 55%, and optimally about 100% sequence identity to the CCD or FLD of NL1.

[0069] The fusion protein can comprise one, two, or more ARF peptide portions that exhibit less than 100% sequence identity to a wild-type ARF peptide portion (an ARF wild-

type CCD or FLD). In such fusion proteins, the biological properties of the ARF peptide portions can be changed in a therapeutically advantageous manner. For example, the removal, substitution, or addition of particular amino acids to the fusion protein FLD can reduce a host immune response to the fusion protein and/or increase the stability of the fusion protein, examples of which are discussed elsewhere herein.

**[0070]** A preferred fusion protein of the invention includes (1) a fibrinogen-like domain that exhibits at least about 65%, preferably at least about 75%, and more preferably at least about 85%, amino acid sequence identity to the fibrinogen-like domain of a first wild-type protein, which binds a receptor that, when activated, promotes or inhibits angiogenesis, and (2) a coiled-coil domain that exhibits at least about 50%, preferably at least about 75%, and even more preferably at least about 85% amino acid sequence identity to the coiled-coil domain of a second wild-type protein, which increases the affinity of the fusion protein for the receptor, promotes formation of a multimer comprising the fusion protein, or both, where the first protein and second protein are different, the first protein and second protein each exhibit at least about 30% overall amino acid sequence identity to Ang-1, and the first protein, the second protein, or both proteins are not Ang-1, Ang-2, Ang-3, or Ang-4.

**[0071]** The first wild-type protein binds a receptor, that, when activated, promotes or inhibits angiogenesis. The first wild-type protein is typically and preferably an ARF, and, most preferably, an ARF that binds and activates a receptor that promotes angiogenesis (e.g., Ang-1). A "receptor" is any protein that interacts with at least one ligand (e.g., a wild-type ARF) to initiate a biological response apart from the receptor-ligand interaction. Receptor activation occurs when the receptor-ligand interaction produces the biological response. Preferably, the receptor is a TIE receptor, and most preferable a TIE-2 receptor.

**[0072]** Receptor binding can be measured using any suitable technique. Simple techniques for determining receptor binding include saturation and competition assays performed with labeled (typically radiolabeled) ligands or putative ligands, which are briefly discussed elsewhere herein. Alternatively, a labeled receptor, or material containing the receptor, can be associated with a filter or a chromatography matrix, and a solution comprising the ligand or putative ligand can be permitted to associate with the receptor or receptor composition, to determine whether receptor binding occurs. Scintillation techniques also are useful for evaluating radiolabeled ligand-receptor interactions. Alternatively, streptavidin/biotin labeling systems, or labeling with fluorescent dyes or peptide portions (e.g., a Green Fluorescent Protein portion), can be used to determine receptor binding. Phage display techniques (such as those described in Cwirla et al., *Proc. Natl. Acad. Sci. USA*, 87, 6378-6382 (1990) and McCafferty et al., *Nature*, 384, 552-554 (1990)) also can be used to identify ligands. Such techniques are known in the art, and, as such, are not discussed in detail herein. Principles and techniques related to ligand-receptor

assays are further described in, e.g., Smisterova et al., *J. Pharm. Biomed. Anal.*, 12(6), 723-45 (1994), Shaw et al., *Curr. Opin. Biotechnol.*, 3(1), 55-58 (1992), Strosberg et al., *Curr. Opin. Biotechnol.*, 2(1), 30-36 (1991), Zoon et al., *J. Pharm. Biomed. Anal.*, 7(2), 147-54 (1989), and Smith et al., *Clin. Chem.*, 26(5), 543-50 (1980), and references cited therein, as well as U.S. Patents 5,480,792 and 5,939,272 (and references cited therein). Commercially available receptor binding assays include, e.g., the HitHunter® assay system (available through DiscoverX (Fremont CA)). Related techniques for measuring receptor binding are known in the art and discussed further herein.

**[0073]** When the first wild-type protein binds the receptor it also activates the receptor, resulting in a biological response that modulates (either increases or decreases) angiogenesis. "Angiogenesis," in the context of the invention, encompasses promoting the formation of new blood vessels (also referred to in the art as neovascularization), e.g., by attracting endothelial cells to promote blood vessel sprouting, promoting blood vessel growth from or within existing blood vessels (such as by increasing the size of existing blood vessels or inducing collateral blood vessel growth from existing blood vessels (also known as vasculogenesis and often referred to as angiogenesis)), promoting blood vessel remodeling, promoting blood vessel maturation, and reducing blood vessel permeability (leakage). Thus, an angiogenic peptide or peptide portion can be any sequence of amino acids that induces the initiation of blood vessel growth at a location not otherwise undergoing angiogenesis, enhances or heightens collateral blood vessel growth in a location already undergoing angiogenesis, or both.

**[0074]** The angiogenic activity of a protein can be determined by any suitable technique. Examples of techniques for measuring angiogenesis include administering the angiogenic protein or DNA encoding the angiogenic protein (preferably in a suitable vector) in the rabbit or rat hind limb models (using a protocol as described in, e.g., Poliakova et al., *J. Thorac. Cardiovasc. Surg.*, 118(2), 339-47 (1999), Rosengart et al., *J. Vasc. Surg.*, 26(2), 302-12 (1997), Walder et al., *J. Cardiovasc. Pharmacol.*, 27, 91-98 (1996), Takeshita et al., *J. Clin. Invest.*, 93(2), 662-70 (1994), and U.S. Patent 6,121,246), and/or the mouse ear model (using a protocol similar to that described in, e.g., Kjosleth et al., *Microsurgery*, 15(6), 390-98 (1994), or as discussed herein in Examples 1, 2, 4, and 5). Similar techniques are discussed in, e.g., Takeshita et al., *J. Clin. Invest.*, 93(20), 662-70 (1994). Other assays for assessing the angiogenic potential of an angiogenic factor include performing exercise tolerance tests (as described in, e.g., Fujita et al., *Circulation*, 77(5), 1022-29 (1988), Kornowski et al., *Am. J. Cardiol.*, 81(7A), 44E-48E (1998), and Rosengart et al., *Circulation*, 100(5), 468-74 (1999)), magnetic resonance imaging (MRI) testing for local perfusion, rest and stress (adenosine) <sup>99m</sup>Tc-sestamibi SPECT tests, rest and stress (dobutamine) echocardiograms, gradient echo tests, intravascular ultrasound (IVUS) (as



described in, e.g., Oshima et al., *Vasc. Med.*, 3(4), 281-90 (1998)), angiography tests, or any combinations thereof, after administration of the putative angiogenic factor to a tissue (preferably a potentially ischemic or ischemic tissue in a mammalian host). Other quantitative angiogenesis activity assays include the corneal pocket assay, capillary number assay, the matrigel angiogenesis/endothelial cell assay, endothelial cell chemotaxis assays, umbilical artery outgrowth assay, choriollantoic membrane development assay, and related assays described in, e.g., Dellian et al., *Am. J. Pathol.*, 149, 59-72 (1996), Folkman, *Cell*, 79, 315-28 (1994), O'Reilly et al., *Cell*, 88, 277-84 (1997), and Ribatti et al., *J. Vasc. Res.*, 34, 455-63 (1997). A more recent assay specifically designed for analytically comparing the angiogenic potential of different factors is described in Wang et al., *Int. J. Mol. Med.*, 6(6), 645-53 (2000). The angiogenesis-inducing capability of a protein also can be determined by comparative measurement of the number of blood vessels, blood vessel density, total blood vessel volume, blood flow measurements, blood pressure ratios, or the like, in a particular tissue to which an angiogenic factor has been administered (as described in, e.g., Sands et al., *Cancer Lett.*, 27(1), 15-21 (1985), Pu, et al., *Circulation*, 88, 208-15 (1993), Bauters et al., *Am. J. Physiol.*, 267, H1263-71 (1994), Takeshita et al., *supra*, Bauters et al., *Circulation*, 91, 2802-09 (1995), Bauters et al., *J. Vasc. Surg.*, 21, 314-25 (1995), and Witzenbichler et al., *Am. J. Pathol.*, 153(2), 381-94 (1998)). Other useful techniques for measuring angiogenesis include those described in U.S. Patents 5,976,782, 5,972,639, and 5,919,759, as well as the angiogenesis assays described in Brown et al., *Nat. Med.*, 7(7), 864-68 (2001), LaForge et al., *Breast J.*, 6(2), 103-107 (2000), Tolsma et al., *J. Cell Biol.*, 122, 497 (1993), and Vogel et al., *J. Cell. Biochem.*, 53, 74 (1993).

[0075] Although the first wild-type protein binds and activates a receptor, the fusion protein FLD does not have to activate the receptor. Thus, the fusion protein can comprise a FLD that binds the receptor that associates with the first wild-type protein, without activating the angiogenic or anti-angiogenic response upon binding. In this respect, the fusion protein can act as an antagonist for a wild-type ARF, competing for binding to at least one of its receptors. Preferably such fusion proteins comprise an FLD that exhibits at least about 90% amino acid sequence identity to Ang-2, and preferably which comprises 100% amino acid sequence identity to the Ang-2 FLD or the Ang-2X FLD. In some cases, the fusion protein can inhibit angiogenesis.

[0076] Where the fusion protein FLD does not exhibit 100% amino acid sequence identity to a wild-type ARF FLD, the FLD will desirably comprise a first amino acid sequence of the sequence pattern Glu Phe/Tyr/His Trp Leu Gly Leu/Asn Glu/Asp Xaa Val/Ile/Leu Xaa Xaa Ile/Leu Xaa<sub>(12-14)</sub> Asp Trp (SEQ ID NO: 39) ("Xaa" represents any amino acid, unless otherwise noted herein, and a "/" between residues indicates that any of the residues divided by the slash is suitable at that position in the sequence). The FLD

preferably comprises a second sequence of the sequence pattern Phe Ser Thr Xaa Asp Xaa Asp Asn/His Xaa<sub>(3-10)</sub> Cys Ala/Ser Xaa<sub>(4)</sub> Gly Gly Trp Trp Xaa<sub>(2-4)</sub> Cys (SEQ ID NO: 40) (subscripted numbers in parentheses herein refer to numbers of residues at a position, subscripted numbers without parentheses identify a particular residue for purposes of discussing preferred residues or residue types present at that position (e.g., "Xaa<sub>(4-5)</sub>" represents that any four or five amino acids may occupy that position in the sequence)). Typically and preferably, the first FLD sequence is positioned N-terminal to the second FLD sequence.

[0077] The first FLD sequence and second FLD sequence are typically and preferably separated by at least about 20 amino acid residues, and more preferably at least about 30-65 amino acid residues. This sequence of amino acids between the first and second FLD sequences (FLD sequence 1 and FLD sequence 2, respectively) desirably comprises a sequence of the pattern Tyr Xaa<sub>1</sub> Leu Arg Leu (SEQ ID NO: 41) or Tyr Xaa<sub>1</sub> Leu Gln (SEQ ID NO: 42), which can be referred to as the first intervening FLD sequence. Typically, the residue at position Xaa<sub>1</sub> in the first intervening FLD sequence will be an Arg, Ser, Lys, Ala, or Gln residue. The fusion protein FLD further preferably includes a second intervening sequence, located N-terminal to the first intervening sequence but C-terminal to FLD sequence 1, of a sequence pattern such as Phe Xaa Xaa His Xaa<sub>1</sub> Gly Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 43), Tyr Xaa Xaa His Xaa<sub>1</sub> Gly Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 44), Phe Xaa Xaa Phe Xaa<sub>1</sub> Gly Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 45), Tyr Xaa Xaa Phe Xaa<sub>1</sub> Gly Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 46), Phe Xaa Xaa His Xaa<sub>1</sub> Glu Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 47), Phe Xaa Xaa Phe Xaa<sub>1</sub> Glu Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 48), Phe Xaa Xaa Phe Xaa<sub>1</sub> Glu Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 49), Tyr Xaa Xaa His Xaa<sub>1</sub> Glu Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 50), and Tyr Xaa Xaa Phe Xaa<sub>1</sub> Gly Xaa<sub>2</sub> Glu Xaa<sub>3</sub> Xaa<sub>4</sub> (SEQ ID NO: 51), where Xaa<sub>1</sub>, typically represents an Ile or Val residue, Xaa<sub>2</sub> typically represents either an Ala, Asp, or Ser residue, Xaa<sub>3</sub> represents a Gln, Glu, or Thr residue, and Xaa<sub>4</sub> represents an Ala, Gly, or Tyr residue. The Glu residue between Xaa<sub>2</sub> and Xaa<sub>3</sub> can be replaced by any other amino acid, although Glu is preferred at this position. The intervening amino acids further preferably comprise a third intervening sequence, positioned N-terminal to the second intervening sequence, but C-terminal to FLD sequence 1, of the pattern Asp/Glu/Ser Asp/Gly Arg/Asn Xaa<sub>1</sub> Xaa<sub>2</sub> Leu/Phe/Tyr Ala/Ile/Leu Xaa<sub>3</sub>, where Xaa<sub>1</sub> typically represents an Ala or Lys residue, Xaa<sub>2</sub> typically represents an Ala, Glu, or Val residue, and Xaa<sub>3</sub> typically represents a Glu or Gln residue. The intervening amino acids typically comprise a fourth intervening sequence, positioned C-terminal to the first intervening sequence, but N-terminal to FLD sequence 2, of one of the following sequence patterns: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Thr Gly Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 52), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Thr Gly Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 53), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Thr Ala Xaa<sub>(0-3)</sub> Ala Gly

(SEQ ID NO: 54), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Thr Ala Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 55), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Val Gly Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 56), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Val Gly Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 57), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Val Ala Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 58), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Val Ala Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 59), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> His Gly Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 60), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> His Gly Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 61), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> His Ala Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 62), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> His Ala Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 63), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Glu Gly Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 64), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Glu Gly Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 65), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Glu Ala Xaa<sub>(0-3)</sub> Ala Gly (SEQ ID NO: 66), Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Glu Ala Xaa<sub>(0-3)</sub> Leu Gly (SEQ ID NO: 67), where Xaa<sub>1</sub> typically represents a Gly, Lys, Ser, or Thr residue, Xaa<sub>2</sub> represents an Ala or Gly residue, and Xaa<sub>3</sub> represents a Phe or Tyr residue. The intervening amino acids will usually comprise a fifth intervening sequence of 9-22 residues of the pattern Xaa<sub>(0-13)</sub> Asp/Xaa Glu/Ser/Val Phe/Pro/Ser/Tyr Leu/Pro/Ser Ser/Trp/Xaa Gly/His/Xaa Asn/Gln/Leu Asn/Gly/Lys/Met Gln/Pro/Thr positioned C-terminal to the fourth intervening sequence but N-terminal to FLD sequence 2. Desirably the intervening sequence maintains the hydrophathy characteristics commonly associated with wild-type ARFs, discussed elsewhere herein.

**[0078]** Preferably, the fusion protein comprises sequences of more than one, and preferably all, of above-described preferred sequence patterns, in their preferred orientation to one another. As such, the fusion protein FLD desirably comprises a sequence of the above-described sequence patterns in the following order (N-terminal to C-terminal): FLD sequence 1 - third intervening sequence - second intervening sequence - first intervening sequence - fourth intervening sequence - fifth intervening sequence - FLD sequence 2.

**[0079]** FLD sequence 1 desirably comprises a sequence of the more particular sequence pattern Phe Ser Thr Xaa<sub>1</sub> Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Gly Gly Trp Trp Phe Asp Ala Cys Gly Xaa<sub>7</sub> Ser Asn Leu Gly (SEQ ID NO: 68), where Xaa<sub>1</sub> preferably represents a Leu or Lys residue, Xaa<sub>2</sub> preferably represents an Ala or Ser residue, Xaa<sub>3</sub> preferably represents a Gln or Leu residue, Xaa<sub>4</sub> preferably represents a Met or a Val residue, Xaa<sub>5</sub> preferably represents a Leu or a Met residue, Xaa<sub>6</sub> preferably represents a Ser or a Tyr residue, and Xaa<sub>7</sub> preferably represents a Leu or a Pro residue. Also preferably, FLD sequence 2 comprises a sequence of the more specific sequence pattern Glu Xaa<sub>1</sub> Trp Leu Gly Asn Glu Xaa Xaa<sub>2</sub> Xaa<sub>(2)</sub> Xaa<sub>3</sub> Thr Xaa Xaa<sub>4</sub> Xaa<sub>(2)</sub> Tyr Xaa Leu Xaa<sub>5</sub> Xaa<sub>6</sub> Glu Leu Xaa Asp Trp Glu Gly (SEQ ID NO: 69), where Xaa<sub>1</sub> preferably represents a His or a Tyr residue, Xaa<sub>2</sub> preferably represents an Ile or a Val residue, Xaa<sub>3</sub> preferably represents an Ile or a Leu residue, Xaa<sub>4</sub> preferably represents an Arg or a Gln residue, Xaa<sub>5</sub> preferably represents an Arg or a Lys residue, and Xaa<sub>6</sub> preferably represents an Ile or Val residue.

[0080] In some situations, a fusion protein comprising an FLD homologous to an angiopoietin FLD is preferred. Such an "angiopoietin-like FLD" desirably exhibits at least about 40%, preferably at least about 50%, and more preferably at least about 65% (e.g., at least about 70%, at least about 80%, at least about 90%, or even at least about 95%) amino acid sequence identity to at least one wild-type angiopoietin ARF. In such aspects, the fusion protein FLD desirably exhibits at least about 40%, preferably at least about 50%, more preferably at least about 60%, and even more preferably at least about 70% (e.g., at least about 80%, at least about 90%, or even at least about 95%) amino acid sequence identity to the Ang-1 FLD.

[0081] Another set of preferred fusion proteins comprise a fibrinogen-like domain that exhibits at least about 30% amino acid sequence identity to the fibrinogen-like domain of Ang-1, and a coiled-coil domain that comprises (1) an amino acid sequence that exhibits at least about 50%, preferably at least about 60%, and more preferably at least about 75% (e.g., at least about 85%, about 90%, or even 100%) amino acid sequence identity to the coiled-coil domain of zapo1, murine FDRG, or both, (2) an amino acid sequence that exhibits at least about 45%, preferably at least about 50%, more preferably at least about 60%, and even more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the coiled-coil domain of NL1, NL5, or both, (3) an amino acid sequence that exhibits at least about 35%, preferably at least about 40%, more preferably at least about 60%, and even more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the coiled-coiled domain of NL8, (4) an amino acid sequence that exhibits at least about 25%, preferably at least about 35%, and more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the coiled-coiled domain of FLS 139, or (5) an amino acid sequence that fulfills any combination of (1)-(4), wherein *in vivo* administration or production (typically by transcription and translation of a fusion protein-encoding polynucleotide) of the fusion protein desirably promotes or inhibits (most preferably promotes) angiogenesis in a mammalian host. Preferably, in such fusion proteins, the fusion protein FLD will exhibit at least about 50%, more preferably at least about 65%, and even more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the Ang-1 FLD or KAP. Desirably, the CCD of such a fusion protein will exhibit less than about 40%, preferably less than about 30%, and even more preferably less than about 20% amino acid sequence identity to the Ang-1 CCD, Ang-2 CCD, Ang-3 CCD, or Ang-4 CCD (except in some instances where it is preferred that the CCD is the Ang-2X CCD), and can even exhibit less than about 40%, less than about 30%, or even less than about 20% amino acid sequence identity to the CCD of any angiopoietin (e.g., Ang-6).

[0082] The angiopoietin-like FLD can be any suitable size, but preferably is about 200-250 amino acids in length, and more preferably about 210-230 amino acids in length. The angiopoietin-like FLD desirably includes a first FLD sequence that is of the more particular sequence pattern Glu His/Tyr Trp Leu Gly Asn Glu Xaa Ile/Val Xaa<sub>(2)</sub> Ile/Leu Thr Xaa Arg/Gln Xaa<sub>(2)</sub> (SEQ ID NO: 70) (ALFLD sequence 1) and a second FLD sequence is of the sequence pattern Phe Ser Thr Lys/Leu Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Ala/Ser Gln/Leu Met/Val Leu/Met Ser/Thr Gly Gly Trp Trp Phe Asp Ala Cys Gly Leu/Pro Ser Asn Leu Gly (SEQ ID NO: 71) (ALFLD sequence 2). ALFLD sequence 2 preferably is positioned C-terminal to ALFLD sequence 1. Preferably, ALFLD sequence 1 is positioned in the N-terminal-most half of the FLD and ALFLD sequence 2 is positioned in the C-terminal-most half (typically in the C-terminal-most third) of the FLD.

[0083] Usually, an intervening amino acid sequence of about 40-60 amino acid residues separate AFLD sequence 1 and ALFLD sequence 2. Also typically, the angiopoietin-like FLD will include a sequence of about 50-60 amino acid residues N-terminal to ALFLD sequence 1 and a sequence of about 30-50 amino acid residues C-terminal to ALFLD sequence 2. Preferably, the portion of the FLD N-terminal to ALFLD sequence 1 will include a sequence of the sequence pattern Gly Gly Xaa<sub>1</sub> Trp Thr Xaa<sub>2</sub> Ile Gln Xaa<sub>3</sub> Arg Glu Xaa<sub>4</sub> Gly Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Phe Gln Arg Xaa Trp Xaa<sub>8</sub> Xaa<sub>9</sub> Tyr Lys Xaa Gly Phe Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> (SEQ ID NO: 72) (ALFLD N-terminus sequence 1), where Xaa<sub>1</sub> preferably is an Arg or a Gly residue, Xaa<sub>2</sub> preferably is a Leu residue, Xaa<sub>3</sub> preferably is an Arg or His residue, Xaa<sub>4</sub> preferably is an Asn or Asp residue, Xaa<sub>5</sub> preferably is a Ser or Thr residue, Xaa<sub>6</sub> preferably is a Leu or Val residue, Xaa<sub>7</sub> preferably is an Asn or Asp residue, Xaa<sub>8</sub> preferably is a Glu or Lys residue, Xaa<sub>9</sub> preferably is an Asp or Glu residue, Xaa<sub>10</sub> preferably is an Asn or Asp residue, Xaa<sub>11</sub> preferably is a Pro or Val residue, Xaa<sub>12</sub> preferably is an Ala or Ser residue, and Xaa<sub>13</sub> preferably is an Arg or Gly residue. An example of a more particularly preferred sequence pattern of the ALFLD N-terminus sequence 1 pattern is Gly Gly Gly Trp Thr Leu Ile Gln Xaa Arg Glu Asp Gly Ser Val Asp Phe Gln Arg Xaa Trp Lys Glu Tyr Lys Xaa Gly Phe Gly Asn Pro Ser Gly (SEQ ID NO: 73). The angiopoietin-like FLD alternatively, or preferably additionally, comprises a sequence N-terminal to ALFLD sequence 1, and more preferably N-terminal to ALFLD N-terminus sequence 1, of the pattern Phe Xaa<sub>1</sub> Asp Cys Ala Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>(2)</sub> Xaa<sub>4</sub> Gly Xaa<sub>(3)</sub> Xaa<sub>5</sub> Gly Xaa<sub>6</sub> Tyr Thr Xaa<sub>7</sub> Xaa<sub>(3)</sub> Asn Xaa Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa Lys Xaa<sub>11</sub> Xaa<sub>12</sub> Cys Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>(3)</sub> (SEQ ID NO: 74) (ALFLD N-terminus sequence 2), where Xaa<sub>1</sub> preferably is an Arg or a Gln residue, Xaa<sub>2</sub> preferably is an Asp or Glu residue, Xaa<sub>3</sub> preferably is an Ile or Val residue, Xaa<sub>4</sub> preferably is an Ala or Ser residue, Xaa<sub>5</sub> preferably is an Asn or Ser residue, Xaa<sub>6</sub> preferably is an Ile or Val residue, Xaa<sub>7</sub> preferably is an Ile or Val residue, Xaa<sub>8</sub> preferably is a Pro or Thr residue, Xaa<sub>9</sub> preferably is a Lys residue, Xaa<sub>10</sub> preferably is

a Glu or Pro residue, Xaa<sub>11</sub> preferably is an Ala or Val residue, Xaa<sub>12</sub> preferably is a Phe or Tyr residue, Xaa<sub>13</sub> preferably is an Asn or Asp residue, and Xaa<sub>14</sub> preferably is a Leu or Met residue. Examples of more particular preferred sequence patterns of the ALFLD N-terminus sequence 2 sequence pattern include Phe Arg Asp Cys Ala Gly Val Xaa Xaa Ser Gly Xaa Xaa Xaa Ser Gly Ile Tyr Thr Ile Xaa Xaa Xaa Asn Xaa Thr Lys Pro Xaa Lys Val Phe Cys Asp Met Xaa Xaa Xaa (SEQ ID NO: 75) and Phe Arg Asp Cys Ala Asp Val Xaa Xaa Ala Gly Xaa Xaa Xaa Ser Gly Ile Tyr Thr Ile Xaa Xaa Xaa Asn Xaa Pro Lys Pro Xaa Lys Val Phe Cys Asn Met Xaa Xaa Xaa (SEQ ID NO: 76).

[0084] The angiopoietin-like FLD desirably comprises a sequence positioned between ALFLD sequence 1 and ALFLD sequence 2 of the sequence pattern Tyr Xaa Leu Xaa<sub>1</sub> Xaa<sub>2</sub> Glu Leu Xaa Asp Trp Glu Gly Xaa Xaa Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa Xaa<sub>5</sub> Tyr Xaa<sub>6</sub> Xaa Phe Xaa Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Glu Xaa Xaa<sub>10</sub> Xaa Tyr Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa Xaa<sub>15</sub> Xaa Xaa<sub>16</sub> Xaa<sub>17</sub> Xaa<sub>18</sub> Ala Gly Xaa<sub>19</sub> Xaa Xaa<sub>20</sub> Ser Xaa<sub>21</sub> Xaa Xaa Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa Xaa (SEQ ID NO: 77) (ALFLD intervening sequence). Preferred residues for the selected variable residues in the ALFLD intervening sequence pattern are set forth in Table 2.

Table 2

Position	Preferred Residues	Position	Preferred Residues
Xaa <sub>1</sub>	Arg or Lys	Xaa <sub>2</sub>	Ile or Val
Xaa <sub>3</sub>	Ala or Thr	Xaa <sub>4</sub>	Ser or Tyr
Xaa <sub>5</sub>	Gln or Leu	Xaa <sub>6</sub>	Asp or Glu
Xaa <sub>7</sub>	Ile or Leu	Xaa <sub>8</sub>	Gly or Ser
Xaa <sub>9</sub>	Asn or Ser	Xaa <sub>10</sub>	Gln or Leu
Xaa <sub>11</sub>	Arg or Ser	Xaa <sub>12</sub>	Ile or Leu
Xaa <sub>13</sub>	Ser	Xaa <sub>14</sub>	Leu or Val
Xaa <sub>15</sub>	Asp or Gly	Xaa <sub>16</sub>	Ser or Thr
Xaa <sub>17</sub>	Gly or Ser	Xaa <sub>18</sub>	Ser or Thr
Xaa <sub>19</sub>	Arg or Lys	Xaa <sub>20</sub>	Asn or Ser
Xaa <sub>21</sub>	Ile or Leu	Xaa <sub>22</sub>	Gln
Xaa <sub>23</sub>	Asn or Gly		

[0085] Preferred examples of more particular sequence patterns of the AFLD intervening sequence pattern include Tyr Xaa Leu Arg Ile Glu Leu Xaa Asp Trp Glu Gly Xaa Xaa Ala Tyr Ser Gln Tyr Asp Xaa Phe Xaa Ile Gly Asn Glu Xaa Gln Xaa Tyr Arg Leu Ser Leu Xaa Gly Xaa Thr Ala Gly Lys Xaa Ser Ser Leu Xaa Xaa Gln Gly Xaa Xaa (SEQ ID NO: 78), Tyr Xaa Leu Arg Ile Glu Leu Xaa Asp Trp Glu Gly Xaa Xaa Ala Tyr Ser Gln Tyr Glu Xaa Phe Xaa Leu Gly Ser Glu Xaa Gln Xaa Tyr Arg Ile Ser Leu Xaa Gly Xaa Thr

Ala Gly Lys Xaa Ser Ser Leu Xaa Xaa Gln Gly Xaa Xaa (SEQ ID NO: 79), and Tyr Xaa Leu Arg Val Glu Leu Xaa Asp Trp Glu Gly Asn Xaa Ala Tyr Ser Gln Tyr Glu Xaa Phe Xaa Leu Gly Ser Glu Xaa Gln Asn Tyr Arg Ile Xaa Val Lys Gly Xaa Ser Gly Ser Ala Gly Arg Xaa Ser Ser Leu Xaa Xaa Xaa Gly Xaa Asp (SEQ ID NO: 80).

[0086] The angiopoietin-like FLD further desirably comprises a sequence positioned C-terminal to ALFLD sequence 2 of the sequence pattern Xaa Xaa<sub>1</sub> Tyr Xaa<sub>(3)</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>(2)</sub> Lys Xaa Xaa<sub>4</sub> Gly Ile Xaa<sub>5</sub> Trp Xaa<sub>6</sub> Tyr Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Leu Xaa Xaa<sub>13</sub> Xaa Xaa<sub>14</sub> Met Met Xaa<sub>15</sub> Xaa<sub>16</sub> Pro Xaa Xaa<sub>17</sub> Xaa (SEQ ID NO: 81) (ALFLD C-terminus sequence 1). Preferred residues for the selected variable residues in ALFLD C-terminus sequence 1 are set forth in Table 3.

Table 3

Position	Preferred Residues	Position	Preferred Residues
Xaa <sub>1</sub>	Tyr or Phe	Xaa <sub>2</sub>	Asp or Gln
Xaa <sub>3</sub>	Asn or His	Xaa <sub>4</sub>	Asn or Asp
Xaa <sub>5</sub>	Arg	Xaa <sub>6</sub>	His or Tyr
Xaa <sub>7</sub>	Phe or Trp	Xaa <sub>8</sub>	Arg or Lys
Xaa <sub>9</sub>	Gly or Phe	Xaa <sub>10</sub>	Pro or Ser
Xaa <sub>11</sub>	Ser	Xaa <sub>12</sub>	Ala or Ser
Xaa <sub>13</sub>	Ala or Gly	Xaa <sub>14</sub>	Arg or Thr
Xaa <sub>15</sub>	Ile or Leu	Xaa <sub>16</sub>	Arg or Phe
Xaa <sub>17</sub>	Asp or Gly		

[0087] Preferred examples of more particular ALFLD C-terminus sequence patterns of the broader ALFLD C-terminus sequence pattern include Xaa Phe Tyr Xaa Xaa Xaa Gln Asn Xaa Xaa Lys Xaa Asn Gly Ile Arg Trp His Tyr Phe Lys Phe Ser Ser Tyr Ala Leu Xaa Ala Xaa Arg Met Met Ile Glu Pro Xaa Asp Xaa (SEQ ID NO: 82), Xaa Tyr Tyr Xaa Xaa Xaa Gln Asn Xaa Xaa Lys Xaa Asn Gly Ile Arg Trp His Tyr Phe Lys Gly Pro Ser Tyr Ser Leu Xaa Ala Xaa Arg Met Met Ile Arg Pro Xaa Asp Xaa (SEQ ID NO: 83), and Met Tyr Tyr Xaa Xaa Xaa Gln Asn Xaa Xaa Lys Xaa Asn Gly Ile Xaa Trp His Tyr Phe Arg Gly Pro Xaa Tyr Ser Leu Xaa Ala Xaa Arg Met Met Ile Arg Pro Xaa Asp Phe (SEQ ID NO: 84).

[0088] The angiopoietin-like FLD can comprise any suitable combination of the above-described sequences, preferably within the pattern (from N-terminus to C-terminus) ALFLD N-terminus sequence 2, ALFLD N-terminus sequence 1, ALFLD sequence 1, ALFLD intervening sequence, ALFLD sequence 2, ALFLD C-terminus sequence. Thus, the angiopoietin-like FLD will desirably comprise a sequence of the overall pattern Phe Xaa Asp Cys Ala Xaa<sub>(5)</sub> Gly Xaa<sub>(4)</sub> Gly Xaa Tyr Thr Xaa<sub>(4)</sub> Asn Xaa<sub>(5)</sub> Lys Xaa<sub>(2)</sub> Cys Xaa<sub>(5)</sub> Gly

Gly Xaa Xaa Trp Thr Xaa Ile Gln Xaa Arg Glu Xaa Gly Xaa<sub>(3)</sub> Phe Gln Arg Xaa Trp Xaa Xaa Tyr Lys Xaa Gly Phe Gly Xaa<sub>(4)</sub> Glu Xaa Trp Leu Gly Asn Glu Xaa<sub>(5)</sub> Thr Xaa<sub>(4)</sub> Tyr Xaa Leu Xaa<sub>(2)</sub> Glu Leu Xaa Asp Trp Glu Gly Xaa<sub>(6)</sub> Phe Xaa<sub>(4)</sub> Glu Xaa<sub>(3)</sub> Tyr Xaa<sub>(10)</sub> Ala Gly Xaa<sub>(3)</sub> Ser Xaa<sub>(7)</sub> Phe Ser Thr Xaa Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Xaa<sub>(5)</sub> Gly Gly Trp Trp Phe Asp Ala Cys Gly Xaa Ser Asn Lys Asn Gly Xaa<sub>(2)</sub> Tyr Xaa<sub>(7)</sub> Lys Xaa<sub>(2)</sub> Gly Ile Xaa Trp Xaa Tyr Xaa<sub>(5)</sub> Tyr Xaa Leu Xaa<sub>(4)</sub> Met Met Xaa<sub>(2)</sub> Pro Xaa<sub>(3)</sub> (SEQ ID NO: 85).

[0089] In other aspects, the fusion protein FLD exhibits desirably exhibits less than about 65% amino acid sequence identity to the Ang-1 FLD, less than about 60% amino acid sequence identity to the Ang-1 FLD, or even less than about 45% amino acid sequence identity to the Ang-1 FLD (e.g., less than about 40% amino acid sequence identity to the Ang-1 FLD). For example, the fusion protein can comprise an FLD that exhibits at least about 60% amino acid sequence identity (e.g., at least about 70%, at least about 80%, or even at least about 90% amino acid sequence identity) to the fibrinogen-like domain of NL4. The fusion protein FLD alternatively can comprise a sequence that exhibits at least about 45% amino acid sequence identity (e.g., 50% amino acid sequence identity), more preferably at least about 60% amino acid sequence identity, even more preferably at least about 75% amino acid sequence identity (e.g., at least about 80% or even at least about 90% amino acid sequence identity) to the fibrinogen like domain of NL1, the fibrinogen-like domain of NL5, the fibrinogen-like domain of NL8, or any combination thereof. Alternatively, the fusion protein FLD can comprise an amino acid sequence that exhibits at least about 40% amino acid sequence identity (e.g., at least about 50%, at least about 70%, or even at least about 90% amino acid sequence identity) to the fibrinogen-like domain of zapo1, the fibrinogen like domain of murine FDRG, or both. In another alternative, the fusion protein FLD can comprise a sequence that exhibits at least about 45% amino acid sequence identity (e.g., at least about 50%, about 60%, about 70%, about 80%, about 90%, or even 100%) to the fibrinogen-like domain of NL3 (SEQ ID NO: 86) or the Hakata antigen (SEQ ID NO: 87) (as described in, e.g., Sugimoto et al., *J. Biol. Chem.* 273 (33), 20721-20727 (1998) and Yae, *Biochim. Biophys. Acta* 1078 (3), 369-376 (1991)). In yet another alternative, the fusion protein FLD can comprise an amino acid sequence that exhibits at least about 30% amino acid sequence identity, preferably at least about 50% amino acid sequence identity, and more preferably at least about 70% amino acid sequence identity (e.g., at least about 80%, about 90%, or about 95% amino acid sequence identity) to the fibrinogen-like domain of FLS 139. The fusion protein FLD also can comprise a sequence that fulfills any combination of the above-described levels of identity to these non-angiopoietin ARF FLDS (e.g., in the case of a chimeric FLD peptide portion derived from two wild-type ARFs).



[0090] A preferred set of fusion proteins, having an angiopoietin-like FLD, comprise (1) an amino acid sequence that exhibits at least about 50%, preferably at least about 60%, and even more preferably at least about 75% (e.g., at least about 80%, about 90%, or even 100%) amino acid sequence identity to the fibrinogen-like domain of NL1, NL5, NL8, or any combination thereof, (2) an amino acid sequence that exhibits at least about 50%, preferably at least about 60%, and more preferably at least about 75% (e.g., at least about 80%, about 90%, or even 100%) amino acid sequence identity to the fibrinogen-like domain of NL4, (3) an amino acid sequence that exhibits at least about 35%, preferably at least about 40%, and more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the fibrinogen-like domain of zapo1, murine FDRG, or both, (4) an amino acid sequence that exhibits at least about 40%, preferably at least about 45%, and more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the fibrinogen-like domain of NL3 or the Hakata antigen, (5) an amino acid sequence that exhibits at least about 25%, preferably at least about 30%, and more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the fibrinogen-like domain of FLS 139, or (6) an amino acid sequence which fulfills any combination of (1)-(5), and a coiled-coil domain that exhibits at least about 30%, preferably at least about 35%, and more preferably at least about 75% (e.g., at least about 80%, at least about 90%, or even about 100%) amino acid sequence identity to the Ang-1 CCD, Ang-2 CCD, Ang-2X CCD, Ang-3 CCD, Ang-4 CCD, or any combination thereof. A particularly preferred subset of this set of fusion proteins comprise a coiled coil domain that exhibits at least about 65%, preferably at least about 75%, and more preferably at least about 85% amino acid sequence identity to the coiled-coil domain of at least one of Ang-1, Ang-2, or Ang-2X. An alternative preferred subset comprise a coiled-coil domain exhibits at least about 50%, more preferably at least about 75%, and even more preferably at least about 85% amino acid sequence identity to the coiled-coil domain of Ang-3, Ang-4, or both.

[0091] In aspects where the fusion protein includes an FLD that is homologous to the NL1 FLD, NL5 FLD, or both wild-type FLDs, the fusion protein FLD desirably contains at least four cysteine residues, which preferably can form inter-FLD disulfide bonds. The NL1/NL5-like FLD further desirably comprises a first sequence of the pattern Gly Gly Trp Xaa<sub>(3)</sub> Gln Xaa Arg Xaa<sub>(2)</sub> Gly Xaa Val Xaa Phe Xaa<sub>(3)</sub> Trp Xaa<sub>(2)</sub> Tyr Xaa<sub>(2)</sub> Gly Phe Gly Xaa<sub>(6)</sub> Trp Leu Gly Xaa Glu Xaa<sub>(4)</sub> Leu Xaa (SEQ ID NO: 88), which preferably is positioned in the N-terminal-most half of the FLD, and a sequence of the sequence pattern Tyr Xaa<sub>(2)</sub> Phe Xaa Leu Xaa<sub>(2)</sub> Glu Xaa<sub>(3)</sub> Tyr Xaa Leu Xaa Leu Gly Xaa<sub>(6-7)</sub> Asp Xaa<sub>(4)</sub> His Xaa<sub>(4)</sub> Phe Xaa Thr Xaa Asp Xaa Asp Xaa<sub>(5)</sub> Cys Ala Xaa<sub>(4)</sub> Gly Xaa<sub>(2)</sub> Trp Tyr Xaa<sub>(2)</sub> Cys

Xaa<sub>(2)</sub> Ser Asn Leu Asn Gly (SEQ ID NO: 89), positioned C-terminal to first sequence. More preferably, the NL1/NL5-like FLD will comprise an amino acid sequence of the pattern Xaa<sub>1</sub> Cys Xaa Gln Xaa<sub>2</sub> Xaa<sub>3</sub> His Xaa<sub>(2)</sub> Ser Xaa<sub>4</sub> Xaa<sub>5</sub> Tyr Xaa<sub>(2)</sub> Lys Pro Glu Asn Xaa<sub>(0-1)</sub> Asn Xaa<sub>(2-4)</sub> Met Gln Xaa<sub>6</sub> Xaa<sub>7</sub> Cys Xaa<sub>8</sub> Xaa<sub>(3)</sub> Asp Xaa<sub>9</sub> Gly Gly Trp Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Gln Xaa<sub>13</sub> Arg Xaa Xaa<sub>14</sub> Gly Xaa<sub>15</sub> Val Asn Phe Xaa<sub>16</sub> Xaa<sub>17</sub> Asn Trp Glu Xaa Tyr Xaa<sub>18</sub> Xaa Gly Phe Gly Asn Ile Asp Xaa<sub>19</sub> Xaa<sub>20</sub> Xaa<sub>21</sub> Trp Leu Gly Xaa<sub>22</sub> Glu Asn Ile Tyr Xaa Leu Xaa<sub>23</sub> Asn Xaa<sub>24</sub> Xaa<sub>(0-1)</sub> Asn Tyr Lys Leu Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub> Glu Asp Xaa<sub>29</sub> Ser Xaa<sub>30</sub> Xaa Lys Val Xaa Ala Xaa<sub>31</sub> Tyr Xaa Ser Phe Arg Leu Glu Pro Glu Ser Glu Xaa Tyr Xaa<sub>32</sub> Leu Arg Leu Gly Xaa Tyr Xaa Tyr Xaa Xaa<sub>33</sub> Asn Ala Xaa<sub>34</sub> Xaa<sub>(0-1)</sub> Asp Xaa<sub>35</sub> Xaa<sub>(2)</sub> Trp His Xaa<sub>36</sub> Gly Lys Gln Phe Xaa<sub>37</sub> Thr Leu Asp Arg Asp Xaa Asp Xaa Tyr Xaa Gly Xaa<sub>38</sub> Cys Ala His Xaa<sub>(2)</sub> Lys Gly Xaa<sub>39</sub> Xaa<sub>40</sub> Trp Tyr Xaa<sub>41</sub> Ala Cys Ala His Ser Asn Leu Asn Gly Xaa<sub>42</sub> Xaa<sub>43</sub> Tyr Arg Gly Gly His Tyr Arg Ser Xaa Xaa<sub>44</sub> Gln Asp Gly Xaa<sub>45</sub> Xaa Trp Ala Glu Xaa Xaa<sub>46</sub> Gly Gly Ser Xaa<sub>47</sub> Xaa<sub>48</sub> Xaa<sub>49</sub> Xaa<sub>50</sub> Xaa Xaa<sub>51</sub> Xaa Met Met Xaa<sub>52</sub> (SEQ ID NO: 90). Preferred residues for the selected variable residues in this NL1/NL5 FLD are set forth in Table 4.

Table 4

Position	Preferred Residues	Position	Preferred Residues
Xaa <sub>1</sub>	Asn or Asp	Xaa <sub>2</sub>	Ala or Leu
Xaa <sub>3</sub>	Asn or Gly	Xaa <sub>4</sub>	Gly or Ser
Xaa <sub>5</sub>	Ile or Val	Xaa <sub>6</sub>	Leu or Val
Xaa <sub>7</sub>	Phe or Trp	Xaa <sub>8</sub>	Asp or Glu
Xaa <sub>9</sub>	Gly or Pro	Xaa <sub>10</sub>	Leu or Thr
Xaa <sub>11</sub>	Ile or Val	Xaa <sub>12</sub>	Ile or Phe
Xaa <sub>13</sub>	Arg or Lys	Xaa <sub>14</sub>	Asp or Ser
Xaa <sub>15</sub>	Leu or Ser	Xaa <sub>16</sub>	Phe or Tyr
Xaa <sub>17</sub>	Arg or Thr	Xaa <sub>18</sub>	Arg or Lys
Xaa <sub>19</sub>	Gly or Ser	Xaa <sub>20</sub>	Asp or Glu
Xaa <sub>21</sub>	Phe or Tyr	Xaa <sub>22</sub>	Asn or Leu
Xaa <sub>23</sub>	Ser or Thr	Xaa <sub>24</sub>	Arg or Gln
Xaa <sub>25</sub>	Arg or Leu	Xaa <sub>26</sub>	Ile or Val
Xaa <sub>27</sub>	Glu or Thr	Xaa <sub>28</sub>	Leu or Met
Xaa <sub>29</sub>	Phe or Trp	Xaa <sub>30</sub>	Asp or Gly
Xaa <sub>31</sub>	Glu or His	Xaa <sub>32</sub>	Arg or Lys
Xaa <sub>33</sub>	Glu or Gly	Xaa <sub>34</sub>	Ala or Gly
Xaa <sub>35</sub>	Ala or Ser	Xaa <sub>36</sub>	Asn or Ser
Xaa <sub>37</sub>	Ser or Thr	Xaa <sub>38</sub>	Asn or Lys
Xaa <sub>39</sub>	Ala or Gly	Xaa <sub>40</sub>	Trp or Tyr
Xaa <sub>41</sub>	Ala or Asn	Xaa <sub>42</sub>	Arg or Val
Xaa <sub>43</sub>	Trp or Tyr	Xaa <sub>44</sub>	His or Tyr
Xaa <sub>45</sub>	Ala or Asn	Xaa <sub>46</sub>	Arg or His
Xaa <sub>47</sub>	His or Tyr	Xaa <sub>48</sub>	Pro or Ser
Xaa <sub>49</sub>	Leu or Tyr	Xaa <sub>50</sub>	Arg or Lys
Xaa <sub>51</sub>	Ala or Val	Xaa <sub>52</sub>	Ile or Leu

[0092] Where the fusion protein comprises a FLD homologous to the zapol FLD, the fusion protein FLD will desirably comprise a sequence of the sequence pattern Arg Asp Cys Gln Glu Leu Phe Gln Xaa<sub>1</sub> Gly Glu Arg Xaa<sub>2</sub> Ser Gly Leu Phe Xaa<sub>3</sub> Ile Gln Pro Xaa<sub>4</sub> Gly Ser Pro Pro Phe Leu Val Asn Cys Xaa<sub>5</sub> Met Thr Ser Asp Gly Gly Trp Thr Val Ile Gln Arg Arg Xaa<sub>6</sub> Xaa<sub>7</sub> Trp Glu Ala Tyr Lys Xaa<sub>8</sub> Gly Phe Gly Asp Pro Xaa<sub>9</sub> Gly Glu Phe Trp Leu Gly Leu Glu Lys Xaa<sub>10</sub> His Ser Ile Xaa<sub>11</sub> Gly Xaa<sub>12</sub> Arg Xaa<sub>13</sub> Ser Xaa<sub>14</sub> Leu Ala Val Gln Leu Xaa<sub>15</sub> Asp Trp Asp Gly Asn Ala Xaa<sub>16</sub> Leu Leu Gln Phe Xaa<sub>17</sub> Xaa<sub>18</sub> His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu Thr Xaa<sub>19</sub> Pro Xaa<sub>20</sub> Ala Xaa<sub>21</sub> Xaa<sub>22</sub> Leu Gly Ala

Thr Thr Val Xaa<sub>23</sub> Pro Xaa<sub>24</sub> Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp  
 Leu Arg Xaa<sub>25</sub> Asp Xaa<sub>26</sub> Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly Thr Cys  
 Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Xaa<sub>27</sub> (SEQ ID NO: 91). Optionally, the zapo1-  
 like FLD sequence can include an additional sequence, N-terminal to this sequence, of the  
 sequence pattern Ser Ile Pro Xaa<sub>28</sub> Gln Arg Gln Xaa<sub>29</sub> Xaa<sub>30</sub> Lys Lys Gly Ile Phe Trp Lys  
 Thr Trp Xaa<sub>31</sub> Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Xaa<sub>32</sub> Leu Ile Gln (SEQ ID NO:  
 92). Preferred residues for the selected variable residues in these zapo1-like FLD sequences  
 are set forth in Table 5.

Table 5

Position	Preferred Residues	Position	Preferred Residues
Xaa <sub>1</sub>	Glu or Val	Xaa <sub>2</sub>	Gln or His
Xaa <sub>3</sub>	Gln or Glu	Xaa <sub>4</sub>	Gln or Leu
Xaa <sub>5</sub>	Glu or Lys	Xaa <sub>6</sub>	His or Leu
Xaa <sub>7</sub>	Asn or Asp	Xaa <sub>8</sub>	Arg or Gln
Xaa <sub>9</sub>	Ala or Asp	Xaa <sub>10</sub>	Gln or His
Xaa <sub>11</sub>	Gln or His	Xaa <sub>12</sub>	Met or Val
Xaa <sub>13</sub>	Met or Thr	Xaa <sub>14</sub>	Asn or Asp
Xaa <sub>15</sub>	Asn or Gly	Xaa <sub>16</sub>	Arg or Gln
Xaa <sub>17</sub>	Arg or Gln	Xaa <sub>18</sub>	Glu or Lys
Xaa <sub>19</sub>	Pro or Ser	Xaa <sub>20</sub>	Ile or Val
Xaa <sub>21</sub>	Ala or Glu	Xaa <sub>22</sub>	Thr or Val
Xaa <sub>23</sub>	Asn or Gly	Xaa <sub>24</sub>	Gln or Glu
Xaa <sub>25</sub>	Asn or Ser	Xaa <sub>26</sub>	Asn or Ser
Xaa <sub>27</sub>	Arg or Gly	Xaa <sub>28</sub>	Leu or Lys
Xaa <sub>29</sub>	Arg or His	Xaa <sub>30</sub>	Arg or Gln
Xaa <sub>31</sub>	Glu or Lys	Xaa <sub>32</sub>	Leu or Met

[0093] The fusion protein FLD can contain any combination of the above-described sequence portions, or peptide portions of such sequence portions. Any of the preferred selected amino acids in the above-described sequences also can desirably be replaced with a functionally homologous and/or weight-based homologous residue (e.g., where a preferred residue at a particular variable (i.e., Xaa) position is an Trp or Phe residue, a Tyr residue at the indicated position, which also is aromatic, is more preferred than other residues, though less preferred than a Trp or Phe residue). This principle applies to all amino acid sequence patterns discussed herein, unless otherwise stated.

[0094] The fusion protein preferably also comprises a coiled-coil domain. The coiled-coil domain can be any suitable coiled-coil domain, preferred features of which, e.g., a substructure comprising an alpha helix comprising a primarily hydrophobic side, are discussed elsewhere herein. For example, the coiled-coil domain can be a parallel coiled-coil, a leucine zipper CCD, a TRAF2 CCD, an antiparallel coiled-coil, or an apolipoprotein A-I CCD. The CCD also can, for example, be a viral ecoprotein CCD or an epidermal growth factor CCD. ARF CCDs and homologs thereof are most preferred.

[0095] Preferably, the coiled-coil domain increases the affinity of the fusion protein for the receptor that the first wild-type protein binds. "Affinity" is a measure of the degree of attractiveness between a ligand and a receptor. Affinity can be measured by any suitable technique. Typically, affinity is characterized by the receptor-ligand equilibrium dissociation constant,  $K_d$ , and/or the maximal specific binding,  $B_{max}$ , which can be empirically determined for a particular ligand-receptor pair by saturation analysis or other analytical techniques.

[0096] The  $K_d$  for a receptor-ligand interaction is the concentration at which 50% of the receptor's ligand binding sites are occupied by a receptor-ligand interaction, and, as such, is a measure of affinity of receptor for a ligand. In general, the lower the  $K_d$  the higher the affinity, as only a small amount of ligand is required to fill half the receptor binding sites in such situations. The  $B_{max}$  is the maximum amount of ligand that can bind to the receptor, and can be used to indicate receptor concentration and/or number of receptors per cell.

[0097] Saturation analysis techniques typically used to determine affinity are known in the art, and, as such, only briefly discussed herein. In a simple saturation analysis, cell membranes containing the receptor, or whole cells comprising the receptor, are incubated in a first set of assays with a range of concentrations of radioligand from a desired low point until an equilibrium or saturation point is reached. A second set of assays are performed under similar conditions except that a large excess of an unlabelled antagonist for the receptor (e.g., a wild-type ARF versus the fusion protein ligand) is added until an equilibrium is reached, such that the ligand is only permitted to bind to nonspecific sites (i.e., sites other than the receptor). The membranes or cells are then passed through a filter that retains the membranes and/or cells. The radioactivity (or other phenomena associated with the label, e.g., fluorescence intensity) is measured with a suitable detector. The bound radioactivity is then plotted as a function of concentration of the ligand to obtain two curves, representing total binding (obtained in the first set of assays), and nonspecific binding (obtained in the second set of assays), respectively. Nonspecific binding is subtracted from total binding to provide a saturation plot. The top of the saturation plot curve is experimentally equal to the number of binding sites in the system (the  $B_{max}$ ), and the concentration at 50% of this maximum is the  $K_d$ . While this technique is effective for

determining the  $K_d$  and  $B_{max}$  for a ligand-receptor interaction, more typically a Scatchard plot (or Rosenthal plot), or even more typically a mathematical model consisting of a saturable hyperbolic component plus a linear non-saturable component, is used to provide an estimate of the  $K_d$  and  $B_{max}$ .

[0098] Alternatively or additionally, affinity can be measured by a competition assay. Briefly, in a competition assay, a single concentration of labeled ligand is used for every assay point (which typically are limited to concentrations below the ligand's  $K_d$  value if known). The level of specific binding of the radioligand is then determined in the presence of a range of concentrations of other competing non-radioactive compounds to measure the potency with which they compete for the binding of the radioligand. The results of the competition assay provide a measure of the relative affinity of competing ligands for a receptor. The data for each competing ligand is usually fitted to a hyperbolic equation from which the  $IC_{50}$  (i.e., the molar concentration of competing ligand (agonist or antagonist) that reduces the specific binding of a radioligand by 50%) can be determined. The  $IC_{50}$  can be correlated to  $K_d$  using the Cheng-Prusoff equation ( $K_i = IC_{50}$  divided by  $1 + [L]/K_d$ , where  $L$  is the concentration of free ligand used in the assay) if the rate of ligand-receptor association ( $K_1$ ) is known.

[0099] Other suitable techniques for measuring the affinity of receptor-ligand pairs are known in the art. Examples of such techniques and related principles are described in, e.g., Chang et al., *Biochim Biophys Acta*, 406(2), 294-303 (1976), Tallarida, *Fed. Proc.*, 41(7), 2323-7 (1982), Levesque et al., *Exp. Cell Res.*, 156(2), 558-62 (1985), Kenakin, *Drugs*, 40(5), 666-87 (1990), Smisterova et al., *J. Pharm. Biomed. Anal.*, 12(6), 723-45 (1995), Van der Graaf et al., *Int. J. Clin. Pharmacol. Ther.*, 35(10), 442-6 (1997), U.S. Patents 3,901,654, 4,251,360, and 5,639,5687, and references cited therein. Alternatively or additionally, the affinity of a ligand for a receptor can be measured by thermodynamic techniques, such as those described in Raffa, *Life Sci.*, 44(4), 245-58 (1989), Pliska, *J. Recept. Signal Transduct. Res.*, 17 (1-3), 495-510 (1999), and Pliska, *J. Recept. Signal Transduct. Res.*, 17(4), 667 (1997). Additional related techniques are described in "Affinity Techniques Enzyme Purification," *Meth. Enzymol.*, 34 (Jakoby and Wilcheck eds. 1974).

[0100] Alternatively, or preferably additionally, the fusion protein CCD promotes formation of a multimer comprising the fusion protein. The multimer can be any collection of two or more non-covalently linked peptides. Thus, the multimer can be a dimer, although typically and preferably the multimer is a trimer or a higher ordered multimer (i.e., a collection of four or more non-covalently linked peptides).

[0101] Multimer formation can be determined by any suitable technique. Several suitable approaches to determining multimer formation are known in the art. A simple technique for assessing multimerization comprises subjecting a first portion of a

composition comprising the putative multimer to size-exclusion chromatography, under conditions where the multimer will not be denatured, to determine the weight of the multimer. Another portion of the composition can be subjected to denaturing SDS-PAGE. If a multimer is formed the weights indicated in the two assays will be different, as the SDS-PAGE gel will exhibit a band reflecting the weight of the monomeric fusion protein, rather than a multimer. Alternatively, two Western blots, one performed under denaturing conditions and the other under non-denaturing conditions can be performed on the multimer containing composition, if an antibody exhibits binding for both the multimer and the monomer. Recently, fluorescent microscopy, mass spectrometry, and light scattering techniques also have been used to determine multimerization. Alternatively, multimer-specific antibody binding assays can be used to assess multimerization.

[0102] The fusion protein CCD can be any suitable size. The CCD will usually be at least about 20, typically about 25-500, more typically about 30-300, even more typically about 30-220 (e.g., at least about 190-210) amino acid residues in length.

[0103] The fusion protein CCD desirably exhibits at least about 25% amino acid sequence identity, preferably at least about 50% sequence identity, more preferably at least about 75% amino acid sequence identity, and even more preferably at least about 90% amino acid sequence identity to the coiled-coil domain of a second wild-type protein, where the second wild-type protein is typically and preferably an ARF, and most preferably is an ARF that promotes angiogenesis *in vivo*.

[0104] In instances where the fusion protein comprises a CCD that is homologous to an angiopoietin, the fusion protein CCD will desirably comprise the sequence Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu Ile Ile Arg Lys Arg Asp Asn (SEQ ID NO: 93). The angiopoietin-like CCD desirably further comprises an amino acid sequence of the sequence pattern Val Asp Gly Xaa Ile Val Xaa<sub>1</sub> Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu Ile Ile Arg Lys Arg Asp Asn Xaa Leu Glu Leu Ser Gln Leu Glu Asn Xaa<sub>2</sub> Ile Leu Asn (SEQ ID NO: 94), where Xaa<sub>1</sub> represents a hydrophobic residue and Xaa<sub>2</sub> represents a basic residue. More particularly still, the angiopoietin-like CCD desirably comprises a sequence of the sequence pattern Leu Glu Xaa Leu Xaa Xaa Xaa Leu Xaa Xaa Gln Lys Arg Xaa Ile Xaa Xaa Leu Gln Xaa Xaa Val Xaa Val Asp Gly Xaa Ile Val Xaa Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu Ile Ile Arg Lys Arg Asp Asn Xaa Leu Glu Leu Ser Gln Leu Glu Asn Xaa Ile Leu Asn Xaa Thr Xaa Xaa Met Leu Xaa Xaa Ala Xaa Xaa Tyr Xaa Xaa Leu Glu Xaa Lys Tyr Xaa Xaa Leu (SEQ ID NO: 95).

[0105] Alternatively, and desirably, where the fusion protein FLD exhibits higher identity to an ARF FLD other than the Ang-1 FLD, Ang-2 FLD, Ang-3 FLD, or Ang-4

FLD, and optionally higher identity to a non-angiopoietin ARF FLD than any angiopoietin FLD, the fusion protein CCD will desirably comprise a sequence of the sequence pattern Tyr Xaa Xaa Asn Ala Xaa Gln Arg Asp Ala Pro Xaa<sub>(1-2)</sub> Glu Xaa Asp Xaa Ser Xaa Gln Xaa Leu Gln Xaa Leu Glu Xaa Xaa Met Glu Asn Xaa Thr Gln Trp Leu Xaa Lys Leu Glu Asn Tyr Ile Xaa Xaa Asn Met Lys Xaa Glu Met Xaa Xaa Ile Gln Gln Asn Ala Val Gln Asn Xaa Thr Ala Xaa Met Xaa Glu Ile Gly Thr Xaa Leu Leu Xaa Gln Thr Ala Glu Gln (SEQ ID NO: 96).

[0106] In another aspect, and desirably where the fusion protein FLD exhibits higher identity to a wild-type ARF FLD other than the Ang-3 or Ang-4 FLD, preferably other than the Ang-1 FLD, Ang-2 FLD, Ang-3 FLD, and Ang-4 FLD, and optionally higher identity to any ARF other than to any angiopoietin, the fusion protein CCD will desirably include a sequence of the sequence pattern Thr Asn Lys Leu Glu Xaa Gln Xaa Leu Xaa Gln Xaa Xaa Xaa Leu Gln Xaa Leu Gln Gly Xaa Asn Xaa Ala Leu Glu Xaa Arg Leu Gln Ala Leu Glu Xaa Xaa Xaa Gln Xaa Xaa Leu Xaa Ser Xaa Xaa Xaa Lys Xaa Xaa Xaa Leu Xaa Xaa Xaa Leu (SEQ ID NO: 97). More preferably, such a fusion protein CCD will comprise a sequence of the sequence pattern Thr Asn Lys Leu Glu Xaa<sub>1</sub> Gln Xaa<sub>2</sub> Leu Xaa<sub>3</sub> Gln Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Leu Gln Xaa<sub>7</sub> Leu Gln Gly Xaa<sub>8</sub> Asn Xaa<sub>9</sub> Ala Leu Glu Xaa<sub>10</sub> Arg Leu Gln Ala Leu Glu (SEQ ID NO: 98), where Xaa<sub>1</sub> preferably represents an Asn or Arg residue, Xaa<sub>2</sub> preferably represents a Leu or Met residue, Xaa<sub>3</sub> preferably represents a Leu or Met residue, Xaa<sub>4</sub> preferably represents an Arg or a Ser residue, Xaa<sub>5</sub> preferably represents an Arg or a Gln residue, Xaa<sub>6</sub> preferably represents a Glu or a Lys residue, Xaa<sub>7</sub> preferably represents an Arg or Gln residue, Xaa<sub>8</sub> preferably represents an Arg or a Gln residue, Xaa<sub>9</sub> preferably represents an Arg or a Ser residue, and Xaa<sub>10</sub> preferably represents a Lys or Thr residue.

[0107] The first wild-type protein and second wild-type protein are different. Preferably, the first wild-type protein and second wild-type protein exhibit less than about 90% overall amino acid sequence identity, preferably less than about 70% overall amino acid sequence identity, even more preferably less than about 50% overall amino acid sequence identity, and optimally less than about 30% overall amino acid sequence identity to each other (e.g., less than about 20%, less than about 15%, or even less than about 10% amino acid sequence identity to each other). Advantageously, at least one, if not both, of the first wild-type protein and second wild-type protein exhibit a higher level of sequence identity to a wild-type ARF other than Ang-1, Ang-2, Ang-3, and Ang-4, or another angiopoietin. Thus, although the first protein and second protein typically exhibit at least about 30% overall amino acid sequence identity to Ang-1, the first wild-type protein, the second wild-type protein, or both proteins, are not Ang-1, Ang-2, Ang-3, or Ang-4.

[0108] The first wild-type protein can be any suitable wild-type ARF. For example, the first wild-type protein can be an angiopoietin (e.g., Ang-1, Ang-2 (SEQ ID NO: 99), Ang-3



(SEQ ID NO: 100), or Ang-4 (SEQ ID NO: 101)), or a non-angiopoietin ARF, such as a muscle ALGF (SEQ ID NO: 102) or liver ALGF (SEQ ID NO: 103) (as described in, e.g., International Patent Application WO 99/67382), NL1 (SEQ ID NO: 104), NL2 (SEQ ID NO: 105), NL3 (SEQ ID NO: 106), NL4 (SEQ ID NO: 107) (which appears to be the same as CDT6, described in International Patent Application WO 01/29085 (SEQ ID NO: 108)), NL5 (SEQ ID NO: 109), NL6 (SEQ ID NO: 110), NL8 (SEQ ID NO: 111), zapo1 (SEQ ID NO: 112), FARP (SEQ ID NO: 113) and HFARP (SEQ ID NO: 114) (as described in, e.g., Lee et al., *Mol. Cells*, 11(1), 100-04 (2001), and Kim et al., *Biochem. J.*, 346 (part 3), 603-10 (2000)), the angiopoietin-like factors described by Peek et al., *Invest. Ophthalmol. Vis. Sci.*, 39(10), 1782-88 (1998) (e.g., Genbank Accession No. NP\_066969), angiopoietin-related protein 5 (SEQ ID NO: 115), angiopoietin related protein 2 (GenBank Accession No. NP\_036053), angiopoietin-like 1 precursor (GenBank Accession No. NP\_004664), the factors recorded at GenBank Accession Nos. BAB27951, XP\_049490, BAB31076, AAK11499, P14448, NP\_082609, AK018113, AF159049\_1, AB056477, XP\_041622, AF169312\_1, AF278699\_1, AAC97965, NP\_065606, AAK83349, AF110520, AF278699, AF379604, and AK019860, fibrinogen/angiopoietin related protein (SEQ ID NO: 116) (as described in Kim et al., *Biochem. J.*, 346, 603-10 (2000)), PPAR gamma (SEQ ID NO: 117), Ang-2A (SEQ ID NO: 118), Ang-2B (SEQ ID NO: 119), and Ang-2C (SEQ ID NO: 120) (as described in, e.g., Mezquita et al., *Biochem. Biophys. Res. Commun.*, 275(2), 643-51 (2000)), Ang2(443) (SEQ ID NO: 121) (as described in, e.g., Kim et al., *J. Biol. Chem.*, 275(24), 18550-56 (2000)), Ang-6 (SEQ ID NO: 122) (as described in, e.g., International Patent Application WO 01/02429), Ang-7 (SEQ ID NO: 123) (as described in, e.g., International Patent Application WO 01/02434), the angiopoietin related proteins described in Yoon et al., *Mol. Cell. Biol.*, 20(14), 5343-9 (2000), a FAIF (as described in, e.g., Kerten et al., *J. Biol. Chem.*, 275(37), 28488-93 (2000)), the angiopoietin related factors described in, or encoded by nucleotide sequences described in, International Patent Applications WO 98/05779, WO 99/15653, WO 99/32515, WO 99/32639, WO 99/40193, WO 99/45135, WO 99/54353 (e.g., sequences 16 and 125), WO 99/62956, WO 99/62925, WO 00/05369 (e.g., the Ang-3 described therein (SEQ ID NO: 124)), WO 00/05241, WO 00/37642, WO 00/52167, WO 00/59938, WO 00/73452 (e.g., sequence 48), WO 01/04264 (e.g., sequence 27), WO 01/05825 (e.g., sequences 1, 3, 5, 11, 13, 14, 45, and 47), WO 01/05972 (e.g., PRO356 (SEQ ID NO: 125)), WO 01/14550 (e.g., PG-3 (SEQ ID NO: 126)), WO 01/36684 (e.g., sequence 40), and variants of such angiopoietins or ARFs (as described in, e.g., Kim et al., *J. Biol. Chem.*, 274, 26523-28 (1999), U.S. Patents 5,521,073, 5,643,755, 5,877,289, 5,879,672, 5,972,338, 6,030,831, 6,057,435, and 6,074,873, and International Patent Applications WO 96/11269, WO 96/31598, WO 99/15653, WO 99/32515, WO 99/45135, WO 99/67382, and WO 01/05825). Other suitable ARFs include the Hakata antigen,

PRO1346 (also known as NL7) (SEQ ID NO: 127), PRO179 (SEQ ID NO: 128), PRO196 (SEQ ID NO: 129), SECP3 (SEQ ID NO: 130) (as described in International Patent Application WO 01/05971), z-alpha5 (as described in, e.g., International Patent Application WO 99/55869), and murine FDRG (SEQ ID NO: 131). In some situations, it is preferred that the first wild-type protein is NL1 or NL5. In other situations, it is preferred that the first wild-type protein is an angiopoietin, and, more preferably, Ang-1. Other preferred ARFs include the factors recorded under GenBank Accession Nos. AI972163 (SEQ ID NO: 132), AI341252 (SEQ NO: 133), and AW293408 (SEQ ID NO: 134). Factors encoded by the sequences recorded under GenBank Accession No. AA048880 also can be suitable, as can the factors recorded at GenBank Accession Nos. AA122061, AB056477, AC092300, AF153606, AF169312, M62290, T57280, T50719, T35448, T11442, and W77823.

[0109] The first wild-type protein alternatively can be a non-ARF protein. For example, the first wild-type protein could be a human fibrinogen chain, a tenascin (e.g., a human tenascin (SEQ ID NO: 135), or a ficolin (e.g., human ficolin (SEQ ID NO: 136)).

[0110] The second wild-type protein can be any suitable protein comprising a CCD (e.g., an epidermal growth factor receptor), but preferably is an ARF (such as any of the aforementioned first wild-type proteins), and most preferably an ARF that promotes angiogenesis *in vivo*. In some aspects, angiopoietin ARFs are preferred, and particularly Ang-1. In other aspects, the second wild-type protein is desirably NL1, FLS 139, NL3, the Hakata antigen, NL4, NL5, NL8, zapo1, or murine FDRG. Where the first wild-type protein is KAP or an angiopoietin, preferred second wild-type proteins include NL1 and NL5.

[0111] The first wild-type protein or second wild-type protein also can be the novel angiopoietin homolog Ang-2X (SEQ ID NO: 137), which is described further herein. Where Ang-2X is the first wild-type protein, the second wild-type protein preferably is Ang-1, Ang-2, Ang-3, or Ang-4, most preferably Ang-1. Alternatively, in such fusion proteins, the second wild-type protein desirably preferably is NL1 or NL5. Where Ang-2X is the second wild-type protein, the first wild-type protein preferably is Ang-1, Ang-2, NL1, or NL5, and most preferably Ang-1.

[0112] A desirable quality of the fusion proteins of the invention is their ability to reduce blood vessel leakage (permeability) when administered or produced *in vivo*. The reduction in blood vessel permeability can be measured relative to the level of permeability in selected blood vessels prior to administration or production of the fusion protein, or, more typically, at a time prior to some selected time after administration or sufficient production of the fusion protein (e.g., at least about 6 hours, about 12 hours, about 1 day, about 2 days, about 3 days, about one week, or longer (e.g., about 2 weeks) after administration of the fusion protein). Alternatively or additionally, the reduction in

permeability can be measured by comparing the level of blood vessel permeability exhibited in blood vessels receiving administration of a VEGF or a polynucleotide encoding a VEGF in the absence of the fusion protein, with blood vessels receiving a substantially identical amount of VEGF in the presence of an effective amount of fusion protein for a similar time period. Preferably, blood vessels affected by the administration or production of the fusion protein exhibit about 90% or less, more preferably about 75% or less, and even more preferably about 50% or less (e.g., about 25% or less) of the vascular permeability exhibited by blood vessels induced or promoted by administration of a VEGF or VEGF-encoding polynucleotide without administration or production of the fusion protein, at about 1 day, about 2 days, about 3 days, about one week, about two weeks, or longer, after administration or production of the fusion protein. The fusion protein of the invention will desirably exhibit such levels of reduced permeability even when co-administered with, or administered closely after (e.g., within about 6 hours, 12 hours, 1 day, or 3 days) administration of a VEGF or VEGF-encoding polynucleotide.

[0113] Blood vessel permeability is the rate at which macromolecules move through a blood vessel wall and outside of the blood vessel. Blood vessel permeability can be determined by any suitable technique, and several techniques are known in the art. One measure of permeability is the lack of force that resists the movement through the blood vessel wall and out of the blood vessel. A simple technique for determining blood vessel permeability involves the application of a labeled, typically radiolabeled, protein that is normally carried in the blood (e.g., FITC labeled, or I<sup>125</sup> labeled, human serum albumin (HSA)), to a blood vessel for a period of time followed by measuring the amount of the labeled protein that enters the tissue surrounding the blood vessel. More sophisticated techniques for assessing blood vessel formation involve MRI, Doppler imaging, and computed tomography. For example, first-pass perfusion imaging MRI can be suitable for assessing vascular perfusion in cardiac tissue *in vivo*. See, e.g., Dranga et al., *J. Mag. Resonance Imaging*, 7, 664-68 (1997) and Wilke et al., *Radiology*, 204, 373-84 (1997). Scanning electron microscopy and/or light microscopy techniques also can be used to assess permeability. See, e.g., Grunt et al., *Scanning Electron Microscopy, part 2*, 575-89 (1986). Other techniques known in the art for assessing blood vessel permeability and related principles are discussed in, e.g., Thurston et al., *Nat. Med.*, 6(4), 460-63 (2000), Bates et al., *Microcirculation*, 6, 83-96 (1999), Thurston et al., *Science*, 286, 2511-14 (1999), Cox et al., *J. Surg. Res.*, 83(1), 19-26 (1999), Carter et al., *Biophys. J.*, 74(4), 2121-28 (1998), Mori et al., *Neurol. Med. Chir.*, 38(11), 697-703 (1998), Kendall et al., *Exp. Physiol.*, 80(3), 359-72 (1995), Adamson et al., *Microcirculation*, 1(4), 251-65 (1994), Yuan et al., *Microvasc. Res.*, 45(3), 269-89 (1993), Olson et al., *J. Appl. Physiol.*, 70(3), 1085-96 (1991), Shibata et al., *Jpn. J. Physiol.*, 41(5), 725-34 (1991), Tompkins, *Am. J. Physiol.*, 260, H1194-1204 (1991),

and Kern et al., *Am. J. Physiol.*, 245(2), H229-36 (1983).

[0114] Typically and preferably, *in vivo* production or administration of the fusion protein also or alternatively is blood vessel maturity (e.g., results in more blood vessels which exhibit greater density and/or structural similarity to mature mammalian blood vessels). The promotion of blood vessel maturity can be determined by comparing selected blood vessels before and after a suitable time after administration or production of the fusion protein (e.g., about 1 day, 2 days, 3 days, one week, or longer) and/or by comparing selected blood vessels that result from the administration of a VEGF or a polynucleotide encoding a VEGF in the absence of the fusion protein versus substantially identical blood vessels that also receive an effective amount of fusion protein (either by production or administration). Particular examples of maturation events include pericyte coating of forming blood vessels and arterialization of newly formed vessels. Generally, immature blood vessels are poorly associated with underlying basement membranes and/or other vessels (as described in, e.g., Dumont et al., *Genes Dev.* 8, 1897-1909 (1994) and Sato et al., *Nature*, 376, 70-74 (1995)). Blood vessel maturation can be assessed using any suitable standard. For example, maturity can be observationally assessed by assessing vessel shape, density, luminal regularity, and vessel opening size (as described in, e.g., Bloch et al., *FASEB J.*, 14(5), 2373-76 (2000)). Maturity also can be assessed by evaluating signal intensity changes in response to hyperoxia (elevated oxygen) and hypercapnia (elevated carbon dioxide), for example by measuring physiological vasodilatory response to carbon dioxide (as described in, e.g., Gilead and Neeman, *Neoplasia*, 1(3), 226-30 (1999)), smooth muscle plasticity, the association of blood vessels with basement membrane or each other, or smooth muscle and non-muscle vascular associated myosin isoform distribution (as described in, e.g., Pauletto et al., *Am. J. Hypertens.*, 7, 661-74 (1994)). Preferably, maturation is determined by assessing recruitment of pericytes to the vasculature, pericyte coating of new vessels, association between the vascular tube and the mural cells, or any combination thereof (as discussed in, e.g., Darland et al., *J. Clin. Invest.*, 103(2), 157-58 (1999), which can be quantified, e.g., by using the microvessel maturation index (MMI) (see, e.g., Goede et al., *Lab. Invest.*, 78(11), 1385-94 (1998)). The *in vivo* administration of the angiogenic fusion protein to a mammalian host typically will result in a higher number or greater concentration of smooth muscle cells, pericytes, mural cells, total endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein limited essentially to the first peptide portion. The increase in number of such cells can be detected using techniques known in the art. Other techniques and principles related to assessing blood vessel maturation are discussed in Koffet et al., *FASEB J.*, 15(2), 447-57 (2001), as well as several other references cited elsewhere herein.

[0115] In a related sense, administration or production of the fusion protein desirably

promotes blood vessel remodeling. "Blood vessel remodeling" includes any type of vascular restructuring not associated with maturation, although the events often typically overlap and/or occur simultaneously in living systems. Typical types of blood vessel remodeling events include increase in vascular mass, vessel wall thickening, vessel enlargement or dilation, alteration in capillary density, vascular bed modification, change in vessel tone, or combinations thereof. Blood vessel remodeling can be assessed through stress state and pressure testing, MRI (e.g., as described in Nikol et al., *Angiology*, 49(4), 251-58 (1998)), *in vivo* ultrasound imaging or histologic analysis (as described in, e.g., Fung et al., *J. Biomech. Eng.*, 115(4B), 453-59 (1993)), and techniques otherwise used to assess angiogenesis (e.g., gradient echo testing). The promotion of blood vessel remodeling can be measured by applying such techniques to selected blood vessels some time before and after a suitable period (e.g., about 1 day, about 2 days, about 3 days, about 1 week, or longer) after administration or production of the fusion protein. ARF-associated blood vessel remodeling is further described in e.g., Goldman-Wohl et al., *Mol. Hum. Reprod.*, 6(1), 81-87 (2000).

[0116] Administration or production of the fusion protein will preferably promote angiogenesis. Tests for assessing whether angiogenesis promoted are discussed above. The assessment of whether administration or production of the fusion protein promotes angiogenesis can be assessed with respect to the tissue, organ, or host of interest, by applying such techniques before and after a suitable time after administration or production of an effective amount of the fusion protein (e.g., about 1 day, about 2 days, about 3 days, about 1 week, or longer).

[0117] Preferably, the fusion protein, when administered or produced in a mammalian host, will exhibit an *in vivo* half-life which is at least about 110%, preferably at least about 125%, and more preferably at least about 150% (e.g., at least about 200%, about 250%, about 300%, about 500%, or more) as long as the half-life of Ang-1. Half-life marks a point where the total amount of fusion protein administered to, or produced in, the tissue or host exhibits a reduction in biological activity of about 50%. The biological activity can be any of the aforementioned biological activities associated with the fusion protein (e.g., promotion of angiogenesis, more particularly reduction of vessel leakage, promotion of vascular maturity, and/or promotion of vascular remodeling). Preferably, the fusion proteins will exhibit a half-life of at least three minutes, desirably at least about four minutes, more preferably at least five minutes, and even more preferably at least ten minutes (e.g., at least about 15, at least about 20, at least about 30, at least about 60, at least about 90, at least about 180, at least about 360, at least about 720 minutes, or even longer) in a mammalian host upon administration (or production). Extended half-life can be obtained by the removal of proteolytically susceptible residues from the ARF peptide

portions. For example, the conversion of Cys<sub>265</sub> in wild-type Ang-1 to Ser<sub>265</sub>, can promote resistance to proteolytic degradation in a fusion protein comprising a modified Ang-1 peptide portion where the residue corresponding to Cys<sub>265</sub> is so modified. In Ang-1, this cysteine is of a 20-residue sequence positioned between the Ang-1 CCD and Ang-1 FLD. The exclusion of this sequence (or at least a portion containing Cys<sub>265</sub>) from the fusion protein, or substitution of this sequence with an alternative "middle" domain sequence (e.g., Val Asn Leu Ser Thr Lys Glu Gly Val Leu Leu Lys Gly Lys Arg Glu Glu Glu Lys (SEQ ID NO: 138)) is expected to result in better half-life than that exhibited in Ang-1. Half-life also can be extended by the addition of a heterologous peptide portion to the fusion protein (e.g., an IgG domain) (as described in, e.g., International Patent Applications WO 98/22577 and WO 00/24782 and/or U.S. Patents 6,121,022 and 6,277,375), by the insertion of sequences that promote N-terminal glycosylation of the fusion protein (as described in, e.g., U.S. Patent 5,218,092), or by administering the fusion protein with a non-proteinaceous polymer, such as those described elsewhere herein.

**[0118]** The fusion protein peptide portions can be associated in any suitable manner. Typically and preferably, the first and second peptide portions will be covalently associated (e.g., by means of a peptide or disulfide bond). The peptide portions can be directly fused (e.g., the C-terminus of the fusion protein CCD can be fused to the N-terminus of the fusion protein FLD through a peptide bond between the two portions). The fusion protein can include any suitable number of modified bonds, e.g., isosteres, within or between the peptide portions. Alternatively, the fusion protein can include a peptide linker between the peptide portions that includes one or more amino acid sequences not forming part of the biologically active peptide portions. Any suitable peptide linker can be used. The linker can be any suitable size. Typically, the linker will be less than about 30 amino acid residues, preferably less than about 20 amino acid residues, and more preferably about 10 or less amino acid residues. Typically the linker will predominantly consist of neutral amino acid residues. Suitable linkers are generally described in, e.g., U.S. Patents 5,990,275, 6,010,883, 6,197,946, and European Patent Application 0 035 384. More particular examples of suitable linkers are provided further herein.

**[0119]** The linker can include one or more cleavage sites to promote separation of linked peptide portions under specific conditions (e.g., exposure to certain proteolytic enzymes) if desired. Examples of such cleavage sites include the Ile Glu Gly Arg linker sequence (SEQ ID NO: 139), which is cleaved by Factor X<sub>a</sub> protease. Other sites can include sequences which are cleaved by, for example, trypsin, enterokinase, collagenase, and thrombin. Alternatively, the cleavage site in the linker sequence can be a site capable of being cleaved upon exposure to a selected chemical or chemical state, e.g., cyanogen bromide, hydroxylamine, or low pH. Additional examples of suitable cleavable linkers are

provided in U.S. Patent 4,719,326.

[0120] Typically and preferably, the first and second peptide portions will be directly fused, or separated by a non-cleavable linker of less than about 10 amino acid residues (e.g., 1-5 amino acid residues).

[0121] Linkers that reduce the immunogenicity of the fusion protein in a mammalian host, preferably a human host, are preferred. Any linker that reduces the immune response of the intended recipient of the fusion protein is suitable in this respect. Preferably, a flexible linker, which does not interfere with the tertiary structure of the fusion protein ARF peptide portions, and preferably which permits the fusion protein to exhibit an overall tertiary structure similar to at least the CCD FLD, and any intervening portions of a wild-type ARF, is used. By not interfering with the tertiary structure of the peptide portions and/or the fusion protein overall, the flexible linker will not configure the fusion protein in a manner such that foreign epitopes are presented to the target's immune system. The flexible linker is desirably immunologically inert in the host system, and addition of it to the fusion protein desirably does not produce epitopes resulting in a strong immunological host response against the fusion protein, and desirably eliminates any sequences that might result in such immune response from the otherwise direct fusion of the first and second peptide portions. Any flexible linker can be used. Typically and preferably the flexible Gly<sub>4</sub>Ser<sub>3</sub> linker or derivative thereof (i.e., a linker comprising the sequence Gly Gly Gly Gly Ser Ser Ser (SEQ ID NO: 140) is used in such fusion proteins. The use of such flexible linkers is described in, e.g., McCafferty et al., *Nature*, 348, 552-554 (1990), Huston et al., *Proc. Natl. Acad. Sci. USA*, 85, 5879-5883 (1988), Glockshuber et al., *Biochemistry*, 29, 1362-1367 (1990), and Cheadle et al., *Molecular Immunol.*, 29, 21-30 (1992). Other glycine-rich flexible linkers also can be suitable, such as the Pro Gly Ile Ser Gly Gly Gly Gly Gly linker (SEQ ID NO: 141), described in Guan et al., *Anal. Biochem.*, 192(2), 262-67 (1991), the Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser linker (SEQ ID NO: 142), described in Huston et al., *Proc. Natl. Acad. Sci. USA*, 85, 5879-5883 (1988), and the Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Lys Glu Phe linker (SEQ ID NO: 143), described in Bird et al., *Science*, 242, 423-26 (1988). Other suitable flexible linkers include the immunoglobulin hinge linkers (as described in, e.g., U.S. Patents 5,672,683 and 6,165,476), and helical peptide linkers (as described in, e.g., U.S. Patent 6,132,992).

[0122] Alternatively, where the first and second peptide portions are directly fused, the fusion protein can be designed such that the intersection ("fusion point") of the FLD and CCD does not generate a sequence which results in a strong immune response against the fusion protein (e.g., as compared to the direct fusion of the corresponding (i.e., most homologous/identical) wild-type ARF peptide portions). Such determinations can be made by using algorithms that identify MHC class I and MHC class II epitope sequences

(preferably through the use of bioinformatics software incorporating such algorithms or through the use of databases which provide listings of such epitopes identified with such algorithms). Any suitable algorithm, database, or program can be used. Examples of such algorithms, programs, and databases include the EPIMER/EPIMAX algorithm developed at the Brown University School of Medicine, the BONSAI algorithm developed at Stanford University, the TEPITOPE algorithm, the Zycos, Inc. "EPIQUEST" database, the SYFPEITHI program (which applies the algorithm of Rammensee et al.), the MAPPP program (available at <http://www.mpiib-berlin.mpg.de/MAPPP/addquery.html>), and the BIMAS program (available at [http://bimas.dcrf.nih.gov/molbio/hla\\_bind/](http://bimas.dcrf.nih.gov/molbio/hla_bind/)), which are variously described in, e.g., Altuvia et al., *Mol. Immunol.*, 31, 1-19 (1994), Brusica et al., *Nuc Acids Res.*, 22, 3663-3665 (1994), Hammer et al., *J. Exp. Med.*, 180, 2353-2358 (1994), Parker et al., *J. Immunol.*, 152, 163-175 (1994), Sturniolo et al., *Adv. Immunol.*, 66, 67-100 (1997), and Cunha-Neto, *Braz. J. Med. Biol. Res.*, 32(2), 199-205 (1999). The amino acid sequence which would result upon the production or production of the fusion protein of interest, particularly the area where the first and second peptide portions intersect and surrounding region (typically about 15 residues or less, more typically about 10 amino acid residues or less, in both directions from the fusion point), can be inputted into such a program, referenced against such databases, or analyzed by similar technique, to determine whether the sequence would result in an undesired host immune response (e.g., formation of a complex with an MHC class I molecule, MHC class II molecule, or both). The polynucleotide sequences encoding the termini of the CCD and/or FLD can be deleted or modified accordingly to obtain a fused sequence that will not induce such an immune response. The insertion of a linker also can prevent such a sequence from being formed.

[0123] Thus, the invention provides a fusion protein wherein the CCD, FLD, or both lack one or more amino acid residues corresponding to residues in their wild-type counterparts near the fusion point (typically within about 20 amino acids or less, more typically within about 10 amino acids or less of the fusion point). Such that administration or production of the fusion protein results in a lower level of host immune response than occurs against an unmodified fusion protein (i.e., a fusion protein comprising a wild-type ARF FLD directly fused to a wild-type ARF CCD). The residues that would result in the immunologically-undesirable amino acid sequence can be removed either through deletion or through non-immunologically equivalent substitutions (which typically will be non-homologous in nature). Typically and preferably, about 15 or less, at the polynucleotide level and more typically about 5 or less of the residues will require deletion or substitution. In some fusion proteins, even a single deletion addition, or substitution will result in the desired reduction in the immunogenicity of the sequence formed by the fusion of the first peptide portion and second peptide portion. By "corresponding" in this context, it is meant



that the deleted/substituted residue is homologous to, or more typically identical to, a sequence occurring in the wild-type peptide, and would align with the residue in the peptide portion's wild-type counterpart in an optimal alignment if present in the fusion protein.

Similar techniques can be applied to fusion proteins that contain a linker, if necessary.

[0124] By using the above-described techniques to modify a wild-type FLD-encoding and/or CCD-encoding sequence, a fusion protein comprising a FLD directly fused to a CCD, where the amino acid sequence within about 10 residues, preferably within about 20 residues, and more preferably within about 30 amino acid residues of the FLD/CCD junction will not form a complex with an MHC Class I molecule, an MHC Class II molecule, or both, *in vivo*, can be obtained. Alternatively, using the above-described techniques, a fusion protein comprising a linker positioned between the fibrinogen-like domain and the coiled-coil domain can be prepared, such that the amino acid sequence within about 15 amino acid residues, preferably about 20 amino acid residues, and more preferably within about 30 amino acid residues of the linker does not form a complex with an MHC Class I molecule, an MHC Class II molecule, or both, when the fusion protein is produced in, or administered to, a mammalian host. "Within about 10 amino acid residues of the linker" refers to the sequence about 5 residues N-terminal of the center of the linker sequence and about 5 amino acid residues C-terminal to the center of the linker sequence.

[0125] Immunogenicity testing of the fusion protein or polynucleotides of the invention also can be assessed using any suitable immunogenicity model prior to administration to the target, particularly where the target of administration is a human, to determine whether the area of fusion will exhibit an acceptable level of immunogenicity upon *in vivo* administration or produced. Reducing exposure to epitope sequences identified by the above-described techniques also can reduce or eliminate the immune response to the fusion protein of the invention. For example, identified epitope sequences or adjacent sequences can be PEGylated (e.g., by insertion of lysine residues to promote PEG attachment) to shield identified epitopes from exposure. Other techniques for reducing immunogenicity of the fusion protein of the invention can be used in association with the administration of the fusion protein include the techniques provided in U.S. Patent 6,093,699.

[0126] Where a linker is incorporated into the fusion protein, the presence of the linker preferably does not impede the biological activity of the FLD, CCD, and more preferably of either domain, and more desirably enhances the biological activity of the separate peptide portions over a direct fusion of the peptide portions (e.g., the promotion of vascular maturation and/or reduction of plasma leakage). Examples of techniques used to assess the effect of linker sequences on the biological activities of fusion proteins are described in, e.g., Newton et al., *Biochemistry*, 35, 545-553 (1995), which can be modified as appropriate for the fusion proteins of the invention (e.g., using the biological assays described elsewhere

herein). It will typically be advantageous for the linker to permit the first ARF peptide portion, second ARF peptide portion, or both ARF peptide portions, to exhibit a secondary and/or tertiary structure similar to that of their native peptide counterparts, which can be assessed using techniques provided herein or similar techniques known in the art.

[0127] The *in vivo* administration or production of fusion protein of the invention desirably promotes angiogenesis, or any aspect thereof (e.g., reduces plasma leakage, promotes vessel maturity, and/or promotes vessel remodeling) more than the administration or production of a wild-type ARF corresponding to one of the ARF peptide portions, and more preferably than the administration or production of either (most preferably both) of the two wild-type ARFs most closely related to the fusion protein's ARF peptide portions under substantially identical conditions and doses. The determination that the fusion protein promotes angiogenesis more than a wild-type ARF can be made by applying any of the techniques described herein for measuring angiogenesis to substantially identical systems (e.g., tissues) separately receiving the wild-type ARF(s) and the fusion protein of the invention.

[0128] The fusion protein can include any suitable number of non-ARF peptide portions. The fusion protein portion can include any number of other elements (e.g., peptide portions) or modifications (e.g., additional amino acid sequences or other peptide fragments), as long as the biological functions (e.g., reduction of vascular permeability) of the fusion protein are not substantially diminished (i.e., not diminished by more than about 20%, preferably not more than about 10%, and even more preferably not at all) over a fusion protein lacking such additional elements. Examples of such elements include sequences encoding proteins for post-translational modification or for binding to a small molecule ligand.

[0129] The fusion protein can comprise any suitable post-translational modifications or modifications. Examples of common and suitable post-translational modifications include carboxylation, glycosylation, hydroxylation, lipid or lipid derivative-attachment, methylation, myristylation, phosphorylation, and sulfation. Other post-translational modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formylation, GPI anchor formation, iodination, oxidation, proteolytic processing, prenylation, racemization, selenoylation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Similar modifications are described in, e.g., Creighton, *supra*, Seifter et al., *Meth. Enzymol.*, 182, 626-646 (1990), and Rattan et al., *Ann. N.Y. Acad. Sci.*, 663, 48-62 (1992). Moreover, the fusion protein can be either a methionine-containing

or methionineless N-terminal variant of any of the fusion proteins described herein. The nature and extent of post-translational modifications is largely determined by the host cell's posttranslational modification capacity and the modification signals present in the polypeptide amino acid sequence. For instance, glycosylation often does not occur in bacterial hosts such as *E. coli*. Accordingly, when glycosylation is desired, a polypeptide should be expressed (produced) in a glycosylating host, generally a eukaryotic cell (e.g., a mammalian cell or an insect cell). Post-translational modifications can be verified by any suitable technique, including, e.g., x-ray diffraction, NMR imaging, mass spectrometry, and/or chromatography (e.g., reverse phase chromatography, affinity chromatography, or GLC). The fusion protein or portion thereof also or additionally can comprise one or more modified amino acids, non-naturally occurring amino acids (e.g.,  $\beta$  amino acids), alternative amino acids (e.g., selenocysteine), or amino acid analogs, such as those listed in the *Manual of Patent Examining Procedure* § 2422 (7th Revision – 2000), which can be incorporated by protein synthesis, such as through solid phase protein synthesis (described in, e.g., Merrifield, *Adv. Enzymol.*, 32, 221-296 (1969)).

[0130] A common additional element present in the fusion protein is a signal sequence, which directs either organelle trafficking (e.g., an endoplasmic reticulum trafficking signal as described in, e.g., U.S. Patent 5,846,540) and/or cell secretion. Such sequences are typically present in the immature (i.e., not fully processed) form of the fusion protein, and are subsequently removed/degraded to arrive at the mature form of the protein. Both naturally occurring and heterologous signal sequences are suitable (e.g., a secretion sequence associated with the protein incorporated in the second peptide portion as discussed herein). For example, a VEGF-A secretion signal sequence Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu Val Leu His His Ala Lys Trp Ser Gln Ala (SEQ ID NO: 144) or a portion thereof, can be used, preferably bound to the N-terminus of the fusion protein CCD, or a sequence N-terminal to the CCD. Such sequences will necessarily vary with the host in which the fusion protein is produced. Examples of heterologous secretion sequences include STII or Ipp for *E. coli*, alpha factor for yeast, and viral signals such as herpes gD for mammalian cells. Further examples of signal sequences are described in, e.g., U.S. Patents 4,690,898, 5,284,768, 5,580,758, 5,652,139, and 5,932,445. Additional signal sequences can be identified using skill known in the art. For example, sequences identified by screening a library can be analyzed using the SignalP program (see, e.g., Nielsen et al., *Protein Engineering*, 10, 1-6 (1997)), or similar sequence analysis software capable of identifying signal-sequence-like domains, or by otherwise analyzing the sequences for features associated with signal sequences, as described in, e.g., European Patent Application 0 621 337.

[0131] Alternatively or, preferably additionally, the fusion protein can comprise a wild-

type ARF variable domain or homolog thereof. An "ARF variable domain" is any amino acid sequence of at least about 10 residues, preferably at least about 20 residues, positioned N-terminal to the wild-type ARF CCD. For example, the fusion protein can comprise the Ang-1 variable region (SEQ ID NO: 145). Such variable domains typically will comprise wild-type ARF signal sequences where the fusion protein comprises a homologous variable domain peptide portion, the homologous variable domain will desirably exhibit at least about 70%, preferably at least about 80%, and more preferably at least about 90% amino acid sequence identity to a wild-type ARF variable domain. The fusion protein variable domain desirably exhibits the highest level of local sequence identity to the same wild-type ARF as the fusion protein CCD or FLD.

[0132] In view of the above, it should be clear that the fusion proteins of the invention include both mature (fully processed) and immature (nascent) peptide portions, particularly where such fusion proteins are produced through the expression of a polynucleotide of the invention. In this respect, a peptide portion of the fusion protein can comprise one or more "propeptide" regions, which are removed during processing. Accordingly, nucleotide sequences encoding such propeptide portions along with the "mature" amino acid sequence associated with the peptide portion are within the scope of the invention.

[0133] Other non-ARF peptide portions that can be included in the fusion protein include binding regions, such as avidin or an epitope, which can be useful for purification and processing of the fusion protein. Examples of such sequences are described in, e.g., International Patent Application WO 00/15823. In addition, detectable markers can be attached to the fusion protein, so that the traffic of the fusion protein through a body or cell can be monitored conveniently. Such markers may include radionuclides, enzymes, fluorophores, small molecule ligands, and the like.

[0134] Recently, the production of fusion proteins comprising a prion-determining domain has been used to produce a protein vector capable of non-Mendelian transmission to progeny cells (see, e.g., Li et al., *J. Mol. Biol.*, 301(3), 567-73 (2000)). The inclusion of such prion-determining sequences in the fusion protein is contemplated, ideally to provide a heritable protein vector comprising the fusion protein that does not require a change in the host's genome.

[0135] The mature fusion protein also can include additional peptide portions which act to promote stability, purification, and/or detection of the fusion protein. For example, a reporter peptide portion (e.g., green fluorescent protein (GFP),  $\beta$ -galactosidase, or a detectable domain thereof) can be incorporated in the fusion protein. Purification facilitating peptide portions include those derived or obtained from maltose binding protein (MBP), glutathione-S-transferase (GST), or thioredoxin (TRX). The fusion protein also or alternatively can be tagged with an epitope which can be antibody purified (e.g., the Flag

epitope, which is commercially available from Kodak (New Haven, Connecticut)), a hexahistidine peptide, such as the tag provided in a pQE vector available from QIAGEN, Inc. (Chatsworth, California), or an HA tag (as described in, e.g., Wilson et al., *Cell*, 37, 767 (1984)).

[0136] The fusion protein can be further modified or derivatized in any suitable manner (e.g., by reaction with organic derivatizing agents). For example, the fusion protein can be linked to one or more nonproteinaceous polymers, typically a hydrophilic synthetic polymer, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylene, as described in, e.g., U.S. Patents 4,179,337, 4,301,144, 4,496,689, 4,640,835, 4,670,417, and 4,791,192, or a similar polymer such as polyvinylalcohol or polyvinylpyrrolidone (PVP). Mimetics of the fusion proteins are also contemplated. Suitable types of peptide mimetics are described in, e.g., U.S. Patent 5,668,110 and the references cited therein. Furthermore, the fusion protein can be modified by the addition of protecting groups to the side chains of one or more the amino acids of the fusion protein. Such protecting groups can facilitate transport of the fusion peptide through membranes, if desired, or through certain tissues, for example, by reducing the hydrophilicity and increasing the lipophilicity of the peptide. Examples of suitable protecting groups include ester protecting groups, amine protecting groups, acyl protecting groups, and carboxylic acid protecting groups, which are known in the art (see, e.g., U.S. Patent 6,121,236). Synthetic fusion proteins of the invention can take any suitable form. For example, the fusion protein can be structurally modified from its naturally occurring configuration to form a cyclic peptide or other structurally modified peptide.

[0137] The fusion protein also can include a non-CCD, or even a non-ARF multimerizing domain or multimerizing component (i.e., a peptide portion which facilitates multimer formation), which permits the fusion protein to form multimers (including dimers) in addition to, or more typically in place of a multimerizing CCD (e.g., in cases where a mutant ARF CCD is incorporated in the fusion protein, a non-multimer forming CCD is incorporated in the fusion protein, or no CCD is incorporated in the fusion protein, such as where the fusion protein is limited to an ARF FLD and some other ARF peptide portion). In such aspects, the fusion protein can comprise any suitable non-ARF multimerization domain. Examples of suitable non-ARF multimerization domains include the human immunoglobulin (IgG) multimerization domains (see, e.g., European Patent Application 0464533) and IgG-derived domains (e.g., the Fc domain as described in, e.g., Johanson et al., *J. Biol. Chem.*, 270, 9459-71 (1995)). Additional modified IgG multimerizing domains and other multimerizing domains are described in International Patent Application WO 00/37642 and the references cited therein. The fusion protein (or polynucleotide encoding the fusion protein) can be administered with a peptide or agent that facilitates multimer

formation (e.g., through promoting formation of disulfide bonds), such as the peptides described in European Patent Application 1 074 563.

**[0138]** The fusion protein can include any suitable multimerization domain which results in the formation of any suitable multimer. The fusion protein multimer can be a heteromultimer (e.g., a heterodimer) or a homomultimer (e.g., a homodimer). Typically and preferably, the fusion protein will form multimers with other fusion proteins of the invention and/or with wild-type ARF peptides (e.g., Ang-1 peptides). Testing for the suitability of any particular multimer combination can be performed using the assays described herein as well as techniques described in, e.g., DiSalvo et al., *J. Biol. Chem.*, 270, 7717-23 (1995), Cao et al., *J. Biol. Chem.*, 271, 3154-62 (1996), and Olofsson et al., *Proc. Natl. Acad. Sci. USA*, 93, 2567-81 (1996)).

**[0139]** In some aspects, the fusion protein contains a multimerization domain which permits dimer formation without permitting formation of higher order multimers. For example, fusion proteins that include the dimerization domains of VEGF<sub>121</sub> or TGF- $\beta$  can limit multimerization to dimer formation.

**[0140]** The fusion protein can comprise one or more heterologous and/or artificial receptor sites, which preferably change the receptor binding profile of the peptide portion, and more preferably localize the fusion protein (or at least the peptide portion) to a specific cell, group of cells, tissue, or tissues. For example, the fusion protein can include an RGD domain or LDV domain of a hemostatic modifier (preferably from a decorsin or a homolog thereof), or other integrin binding domain, selectin binding domain, or similar binding domain (e.g., a laminin, fibrinogen, and/or fibronectin binding domain), examples of which are described in U.S. Patent Application 09/832,355 and references cited therein.

**[0141]** The invention further provides polynucleotides including at least one nucleotide sequence which, when expressed in a cell permissive for expression of the nucleotide sequence, result in the production of the fusion protein. The polynucleotide sequence can be any suitable sequence (e.g., single stranded or double stranded RNA, DNA, or combinations thereof) and can include any suitable nucleotide base, base analog, and/or backbone (e.g., a backbone formed by, or including, a phosphothioate, rather than phosphodiester, linkage). Examples of suitable modified nucleotides which can be incorporated in the polynucleotide sequence are provided in the *Manual of Patent Examining Procedure* § 2422 (7th Revision – 2000). The polynucleotide sequence can be any suitable length (e.g., about 300 nt, about 600 nt, about 1200 nt, about 2000 nt or even larger). The polynucleotide sequence can be any sequence that results in the fusion protein being produced upon expression. As such, the polynucleotide sequence is not limited to sequences that directly code for production of the fusion protein. For example, the polynucleotide can comprise a sequence which results in the fusion protein through intein-

like expression (as described in, e.g., Colson and Davis, *Mol. Microbiol.*, 12(3), 959-63 (1994), Duan et al., *Cell*, 89(4), 555-64 (1997), Perler, *Cell*, 92(1), 1-4 (1998), Evans et al., *Biopolymers* 51(5), 333-42 (1999), and de Grey, *Trends Biotechnol.*, 18(9), 394-99 (2000)), or a sequence which contains self-splicing introns (or other self-spliced RNA transcripts) which form the peptide portions and/or the fusion protein (as described in, e.g., U.S. Patent 6,010,884). The polynucleotides also can comprise sequences which result in other splice modifications at the RNA level to produce an mRNA transcript encoding the fusion protein and/or at the DNA level by way of trans-splicing mechanisms prior to transcription (as described in, e.g., Chabot, *Trends Genet.*, 12(11), 472-78 (1996), Cooper, *Am. J. Hum. Genet.*, 61(2), 259-66 (1997), and Hertel et al., *Curr. Opin. Cell. Biol.*, 9(3), 350-57 (1997)). RNA based vectors may include removal of regions which promote degradation in the absence of hypoxia, e.g., by removal of the mRNA 3' and/or 5' UTRs (see Dibbens et al., *Mol. Biol. Cell.*, 10, 907-19 (1999)) or portion thereof, e.g., the AU rich hairpin structure region of the 3' UTR (see, e.g., Pages et al., *J. Biol. Chem.* (published on June 9, 2000 as manuscript M002104200 – American Society for Biochemistry and Molecular Biology, Inc.), and Levy, *J. Biol. Chem.*, 271, 25492-25497 and 2746-2753 (1996)), particularly where RNA vectors are administered in the absence of hypoxic conditions. The polynucleotide can comprise one or more sequences encoding a fusion protein wherein the fusion protein-encoding sequence or a portion thereof is codon optimized, i.e., codon frequency optimized and/or codon pair (i.e., codon context) optimized for a particular species (e.g., humans, either by optimizing a non-human or human sequence by replacement of "rare" human codons based on codon frequency, such as by using techniques such as those described in Buckingham et al., *Biochimie*, 76(5), 351-54 (1994) and U.S. Patents 5,082,767, 5,786,464, and 6,114,148). For example, the polynucleotide encoding the fusion protein can comprise a codon optimized human Ang-1 FLD gene sequence (SEQ ID NO: 146) or a codon optimized human Ang-1 CCD gene sequence (SEQ ID NO: 147). Additionally, codon optimized sequences for particular peptides can be obtained by subjecting the amino acid sequences of such peptides to backtranslation using a suitable program, such as the Entelechon backtranslation tool (available at <http://www.entelechon.com/eng/backtranslation.html>). Partially codon optimized sequences also can be used, such as codon sequences where only some or all of the "rarest" sequences (for the particular organism of interest) are removed. For example, the polynucleotide can comprise an ARF peptide portion-encoding sequence (e.g., an Ang-1 CCD or FLD sequence) where at least one (preferably all) of the Ala-encoding GCA and/or GCT codons in the sequence are replaced with GCC (but GCG codons are retained), at least one (preferably all) of the Gly-encoding GGC codons in the sequence is replaced with GGG, at least one (preferably all) of the Asn-encoding AAT codons in the sequence is replaced with AAC, at least one

(preferably all) of the Pro-encoding CCA codons in the sequence is replaced with CCG, at least one (preferably all) of the Arg-encoding AGA codons is replaced with CGG, and at least one (preferably all) of the Ser-encoding AGC codons is replaced with TCG. Replacement of such rare codons can be accomplished using any more frequently expressed codons, as desired and appropriate.

[0142] Because the fusion protein will desirably comprise a FLD that is homologous to a first ARF and a CCD that is homologous to a second ARF, it is preferred that the fusion protein's FLD, CCD, or both are encoded by a nucleotide sequence having a complement that hybridizes to the ARF peptide portion's nearest (i.e., most related based on overall polynucleotide sequence identity, amino acid sequence identity, or both) wild-type ARF-encoding counterpart. For example, in a polynucleotide encoding a fusion protein comprising an Ang-1 homolog FLD portion and a NL2 homolog CCD portion, the Ang-1 FLD portion desirably is encoded by a nucleotide sequence having a complement which hybridizes with a wild-type Ang-1 gene under at least moderate stringency conditions (preferably high stringency conditions), the NL2 CCD portion desirably is encoded by a polynucleotide having a complement which hybridizes with a wild-type NL2 gene under at least moderate stringency conditions (preferably high stringency conditions), or, most desirably, the polynucleotide hybridizes to both wild-type Ang-1 and wild-type NL2 gene sequences under such conditions.

[0143] Where the polynucleotide encodes a fusion protein comprising a peptide portion that exhibits 100% amino acid sequence identity to a wild-type ARF peptide portion, the nucleic acid sequence encoding the peptide portion can comprise a portion of the naturally occurring gene encoding the wild-type ARF (a wild-type ARF gene fragment) encoding the wild-type peptide portion. The polynucleotide can comprise any suitable wild-type ARF gene fragment, or combinations of wild-type ARF gene fragments. Preferably, the polynucleotide comprises a wild-type gene fragment encoding a wild-type ARF FLD fused to a wild-type gene fragment encoding a wild-type ARF CCD. For example, the polynucleotide can comprise the Ang-1 FLD-encoding sequence (SEQ ID NO: 148), the Ang-1 CCD-encoding sequence (SEQ ID NO: 149), the Ang-2 FLD-encoding sequence, the Ang-2 CCD-encoding sequence (SEQ ID NO: 150), the NL1 FLD-encoding sequence (SEQ ID NO: 151), or the NL5 FLD-encoding sequence (SEQ ID NO: 152). Sequences identical to those in the wild-type genes for Ang-3 (SEQ ID NO: 153), Ang-4 (SEQ ID NO: 154), Ang-6 (SEQ ID NO: 155), Ang-2A (SEQ ID NO: 156), Ang-2B (SEQ ID NO: 157), Ang-2C (SEQ ID NO: 158), Ang-2X (SEQ ID NO: 159), NL2 (SEQ ID NO: 160), NL3 (SEQ ID NO: 161), the Hakata antigen, NL4 (SEQ ID NO: 162), NL6 (SEQ ID NO: 163), NL8 (SEQ ID NO: 164), FLS 139 (SEQ ID NO: 165), zapo1 (SEQ ID NO: 166), or murine FDRG, can be suitable. Other ARF gene fragments in the patent documents and publications known in



the art, such as those incorporated herein by reference, also can be suitable.

[0144] Alternatively, the fusion protein-encoding polynucleotide can comprise a nucleic acid sequence that exhibits less than 100% polynucleotide sequence identity to such a wild-type gene fragment, but which still encodes a peptide portion that exhibits 100% amino acid sequence identity to the wild-type ARF peptide portion. For example, the polynucleotide sequence can comprise (1) a nucleic acid sequence that exhibits at least about 35%, desirably at least about 50%, preferably at least about 60%, and more preferably at least about 70% (e.g., at least about 80%, at least about 90%, or at least about 95%) polynucleotide sequence identity (either local or overall) to such a wild-type gene fragment, (2) a nucleic acid sequence which hybridizes under at least moderate stringency conditions (preferably high stringency conditions) to the wild-type gene fragment, or (3) a sequence that does not hybridize to and/or exhibit such levels of identity to the gene fragment due to the presence of other sequences that do not affect the produced protein product (e.g., degenerate sequences, sequences that are self-spliced out of the RNA transcript encoded by the nucleic acid sequence, or intein-like expression pattern sequences) but nonetheless when transcribed and translated results in the production of the protein product encoded by the wild-type gene fragment.

[0145] The polynucleotide also can comprise one or more nucleic acid sequences encoding any of the ARF peptide portion homologs described elsewhere herein. Polynucleotide sequences encoding such ARF peptide homologs can be obtained through constructing such sequences based on the desired ARF peptide homolog amino acid sequence.

[0146] Alternatively, ARF homologs or ARF peptide portion homologs (e.g., homologous CCDs and/or FLDs, even in non-ARF peptides) can be obtained by screening polynucleotide libraries (e.g., a genomic library, cDNA library, or sublibrary thereof). For example, the DNA of animal species can be screened to identify ARF homologs or ARF peptide portion homologs. Such screening can be performed by any suitable technique, including, e.g., screening the libraries with polynucleotide probes under conditions wherein hybridization to ARF homolog-encoding polynucleotides is likely to occur (e.g., under at least moderately stringent conditions). Such screening can be performed in a human DNA or cDNA library (e.g., to identify novel ARF splice variants or yet undiscovered ARF homologs), or in a polynucleotide library obtained from other species, preferably other mammalian species (e.g., *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hvlobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadrins*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*, *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Orystolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*).

Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to perform chromosomal screening for ARF homolog-encoding genes. Pools of protein candidates can be similarly screened for ARF homologs using standard biochemical and proteomics-related techniques (e.g., the yeast two hybrid system as described in, e.g., Mendelsohn and Brat, *Curr. Opin. Biotech.*, 5, 482-86 (1994), and/or affinity chromatography (e.g., using a TIE receptor or portion thereof)).

[0147] The fusion protein ARF peptide portions can be identical to, or homologous to, wild-type ARF peptide portions of any animal. The fusion protein's ARF peptide portions can be derived from, or most closely related to, wild-type ARF peptide portions of different animals (e.g., the fusion protein can include a CCD that exhibits 100% identity to a murine ARF CCD and a FLD that exhibits 100% identity to a human ARF FLD). The reference to any ARF (or peptide portion or related polynucleotide) herein encompasses both the human protein (or other particular animal, e.g., mice in the case of murine FDRG) and all orthologs thereof unless otherwise specified. Thus, for example, an "Ang-1 FLD" encompasses both the human Ang-1 FLD and the murine Ang-1 FLD.

[0148] Polynucleotides comprising sequences encoding novel ARF peptide portions, particularly sequences encoding peptide portions homologous to, but not identical with, wild-type ARF peptide portions also can be generated through inducing mutations in known ARF-encoding polynucleotides (e.g., a wild-type Ang-1, Ang-2, Ang-2X, NL1, or NL5 gene fragment). For example, ARF homolog peptide portion-encoding polynucleotides can be obtained through application of site-directed mutagenesis (as described in, e.g., Edelman et al., *DNA*, 2, 183 (1983), Zoller et al., *Nucl. Acids Res.*, 10, 6487-5400 (1982), and Veira et al., *Meth. Enzymol.*, 153, 3 (1987)), alanine scanning, or random mutagenesis, such as iterated random point mutagenesis induced by error-prone PCR, chemical mutagen exposure, or polynucleotide expression in mutator cells (see, e.g., Bornscheuer et al., *Biotechnol. Bioeng.*, 58, 554-59 (1998), Cadwell and Joyce, *PCR Methods Appl.*, 3(6), S136-40 (1994), Kunkel et al., *Methods Enzymol.*, 204, 125-39 (1991), Low et al., *J. Mol. Biol.*, 260, 359-68 (1996), Taguchi et al., *Appl. Environ. Microbiol.*, 64(2), 492-95 (1998), and Zhao et al., *Nat. Biotech.*, 16, 258-61 (1998)). Suitable primers for PCR-based site-directed mutagenesis or related techniques can be prepared by the methods described in, e.g., Crea et al., *Proc. Natl. Acad. Sci. USA*, 75, 5765 (1978). The application of site-directed mutagenesis to produce novel ARF peptide portion variants can be based on a modification of the techniques provided in, e.g., Shortle et al., *Ann. Rev. Genet.*, 15, 288-94 (1981), Keyt et al., *J. Biol. Chem.*, 271, 5638-46 (1996), and Ki et al., *J. Biol. Chem.*, 275(38), 29823-28 (2000).

[0149] Other polynucleotide mutagenesis methods useful for producing novel ARF homolog peptide portions include PCR mutagenesis techniques (as described in, e.g., Kirsch

et al., *Nucl. Acids Res.*, 26(7), 1848-50 (1998), Seraphin et al., *Nucl. Acids Res.*, 24(16), 3276-7 (1996), Caldwell et al., *PCR Methods Appl.*, 2(1), 28-33 (1992), Rice et al., *Proc. Natl. Acad. Sci. USA*, 89(12), 5467-71 (1992) and U.S. Patent 5,512,463), cassette mutagenesis techniques based on the methods described in Wells et al., *Gene*, 34, 315 (1985), phagemid display techniques (as described in, e.g., Soumillion et al., *Appl. Biochem. Biotechnol.*, 47, 175-89 (1994), O'Neil et al., *Curr. Opin. Struct. Biol.*, 5(4), 443-49 (1995), Dunn, *Curr. Opin. Biotechnol.*, 7(5), 547-53 (1996), and Koivunen et al., *J. Nucl. Med.*, 40(5), 883-88 (1999)), reverse translation evolution (as described in, e.g., U.S. Patent 6,194,550), saturation mutagenesis described in, e.g., U.S. Patent 6,171,820), PCR-based synthesis shuffling (as described in, e.g., U.S. Patent 5,965,408) and recursive ensemble mutagenesis (REM) (as described in, e.g., Arkin and Yourvan, *Proc. Natl. Acad. Sci. USA*, 89, 7811-15 (1992), and Delgrave et al., *Protein Eng.*, 6(3), 327-331 (1993)). Alternatively, ARF peptide portion homolog-encoding polynucleotides can be pre-designed and synthetically produced using techniques such as those described in, e.g., Itakura et al., *Annu. Rev. Biochem.*, 53, 323 (1984), Itakura et al., *Science*, 198, 1056 (1984), and Ike et al., *Nucl. Acid Res.*, 11, 477 (1983). For example, sequence analysis of a number of related ARFs (e.g., a number of angiopoietins) can be subjected to sequence analysis (e.g., using CLUSTAL W) to identify an amino acid consensus sequence that can be used to design novel DNAs based on the genetic code (e.g., by subjecting the consensus sequence to reverse translation analysis). Further details regarding the above-described techniques are described in Sambrook et al., and Ausubel et al., *supra*.

[0150] Alternatively, ARF homolog peptide portion-encoding polynucleotides can be generated through directed evolution techniques (e.g., polynucleotide shuffling). Examples of such techniques are described in, e.g., Stemmer, *Nature*, 370, 389-91 (1994), Cherry et al., *Nat. Biotechnol.* 17, 379-84 (1999), and Schmidt-Dannert et al., *Nat Biotechnol.*, 18(7), 750-53 (2000). Preferably, shuffling of the ARF-encoding sequence is performed in combination with staggered extension (StEP), random primer shuffling, backcrossing of improved variants, or any combination thereof, e.g., as described in Zhao et al., *supra*, Cherry et al., *supra*, Arnold et al., *Biophys. J.*, 73, 1147-59 (1997), Zhao and Arnold, *Nucl. Acids Res.*, 25(6), 1307-08 (1997), and Shao et al., *Nucl. Acids Res.*, 26, 681-83 (1998). Alternatively, the incremental truncation for the creation of hybrid enzymes (ITCHY) method (see, e.g., Ostermeier et al., *Nat. Biotechnol.*, 17(12), 1205-09 (1999)) can be applied to combinations of ARF-encoding genes or gene fragments to produce novel ARF-encoding or ARF peptide portion-encoding polynucleotides. Another set of techniques for introducing diversity into a library of homologs are provided in U.S. Patents 6,159,687 and 6,228,639.

[0151] The biological activity of the products of molecular evolution are expected to

vary, and, accordingly, some screening for biological activity of the directed evolution product can be required to ensure the novel ARF homolog peptide portion-encoding polynucleotide is suitable for incorporation in the fusion protein and/or fusion protein-encoding polynucleotides of the present invention. Any suitable assay for measuring the desired biological activity of a molecule can be used, including the techniques described herein with respect to the fusion proteins of the invention (e.g., antibody reactivity, receptor binding, induction of angiogenesis or preferred aspects thereof (e.g., promoting vascular maturation and/or reducing plasma leakage)). In this manner, with a routine amount of experimentation, novel ARF homolog peptide portions can be generated which are suitable for incorporation in the fusion protein-encoding polynucleotide.

**[0152]** Preferably, in addition to the nucleic acid sequence which, when expressed, results in the fusion protein (the "fusion protein nucleic acid sequence"), the polynucleotide further includes one or more suitable "expression control sequences" operably linked to the sequence encoding the fusion protein. An expression control sequence is any nucleotide sequence that assists or modifies the expression (e.g., the transcription, translation, or both) of the nucleic acid encoding the angiogenic sequence. The expression control sequence can be naturally associated with a polynucleotide encoding any ARF peptide portion of the fusion protein (e.g., an Ang-1 promoter), or can comprise a heterologous element with respect to such polynucleotide sequences (e.g., a myocardin cardiac tissue regulator sequence or a desmin locus control region (LCR), both of which are associated with control of muscle gene expression). For example, the fusion protein nucleic acid sequence can be operably linked to a constitutive promoter (e.g., the Rous sarcoma virus long terminal repeat (RSV LTR) promoter/enhancer or the cytomegalovirus major immediate early gene (CMV IE) promoter, which is particularly preferred), an inducible promoter, (e.g., a growth hormone promoter, metallothionein promoter, heat shock protein promoter, E1B promoter, hypoxia induced promoter, radiation inducible promoter, or adenoviral MLP promoter and tripartite leader), an inducible-repressible promoter, a developmental stage-related promoter (e.g., a globin gene promoter), or a tissue specific promoter (e.g., a smooth muscle cell  $\alpha$ -actin promoter, VEGF receptor promoter, myosin light-chain 1A promoter, or vascular endothelial cadherin promoter). In some instances, host-native promoters are preferred over non-native promoters (e.g., a human beta actin promoter or EF1 $\alpha$  promoter driving expression of the fusion protein nucleic acid sequence can be preferred in a human host), particularly where strict avoidance of gene expression silencing due to host immunological reactions is desirable. The polynucleotide can include expression control sequences wherein one or more regulatory elements have been deleted, modified, or inactivated. The polynucleotide also or alternatively can include a bi-directional promoter system (as described in, e.g., U.S. Patent 5,017,478) linked to multiple genes of interest (e.g., multiple

fusion protein encoding genes). Other suitable promoters and principles related to the selection, use, and construction of suitable promoters are provided in, e.g., Werner, *Mamm. Genome*, 10(2), 168-75 (1999), Walther et al., *J. Mol. Med.*, 74(7), 379-92 (1996), Novina, *Trends Genet.*, 12(9), 351-55 (1996), Hart, *Semin. Oncol.*, 23(1), 154-58 (1996), Gralla, *Curr. Opin. Genet. Dev.*, 6(5), 526-30 (1996), Fassler et al., *Methods Enzymol.*, 273, 3-29 (1996), Ayoubi et al., 10(4), *FASEB J.*, 10(4), 453-60 (1996), Goldsteine et al., *Biotechnol. Annu. Rev.*, 1, 105-28 (1995), Azizkhan et al., *Crit. Rev. Eukaryot. Gene Expr.*, 3(4), 229-54 (1993), Dynan, *Cell*, 58(1), 1-4 (1989), Levine, *Cell*, 59(3), 405-8 (1989), and Berk et al., *Annu. Rev. Genet.*, 20, 45-79 (1986), as well as U.S. Patent 6,194,191. In some aspects, radiation-inducible promoters such as those described in described in U.S. Patents 5,571,797, 5,612,318, 5,770,581, 5,817,636, and 6,156,736 can be suitable. In other instances, ecdysone and ecdysone-analog-inducible promoters (ecdysone-analog-inducible promoters are commercially available through Stratagene (LaJolla CA)). Other suitable commercially available inducible promoter systems include the inducible Tet-Off or Tet-on systems (Clontech, Palo Alto, CA). As an alternative to a promoter, particularly in RNA vectors and constructs, the nucleic acid sequence and/or vector can comprise one or more internal ribosome entry sites (IRESs), IRES-encoding sequences, or RNA sequence enhancers (Kozak analogs), such as the tobacco mosaic virus omega prime sequence.

**[0153]** The polynucleotide sequence also or alternatively can comprise an upstream activator sequence (UAS), such as a Gal4 activator sequence (as described in, e.g., U.S. Patent 6,133,028) or other suitable upstream regulatory sequence (as described in, e.g., U.S. 6,204,060). The polynucleotide can include any other expression control sequences (e.g., enhancers, termination sequences, initiation sequences, splicing control sequences, etc.). Typically, the polynucleotide will typically include a Kozak consensus sequence, which can be a naturally occurring or modified sequence such as the modified Kozak consensus sequences described in U.S. Patent 6,107,477. The polynucleotide can further comprise site-specific recombination sites, which can be used to modulate transcription of the polynucleotide, as described in, e.g., U.S. Patents 4,959,317, 5,801,030 and 6,063,627, European Patent Application 0 987 326 and International Patent Application WO 97/09439.

**[0154]** The polynucleotide can include or consist of any suitable fusion protein nucleic acid sequence. Preferred fusion protein nucleic acid sequences include nucleotide sequences which, when expressed, result in the production of the above-described fusion proteins, the polynucleotide can comprise any number of transcriptionally inert sequences (e.g., an intron). The polynucleotide can contain any suitable number of copies of the fusion protein-encoding nucleic acid sequence.

**[0155]** Preferably, the polynucleotide comprises a second nucleotide sequence that, when expressed, produces a second protein which modulates, and preferably promotes,

angiogenesis, bone growth, wound healing, or any combination thereof, and most preferably promotes angiogenesis, particularly where the fusion protein also promotes angiogenesis. The second nucleotide sequence can encode, for example, a receptor that interacts, and preferably is activated by the fusion protein FLD (e.g., a TIE-2 receptor). In this respect, the polynucleotide can include any suitable number of protein-encoding sequences. Alternatively, the second nucleotide sequence can encode for a polynucleozyme (e.g., a ribozyme or DNAzyme) or for the production of an inhibitory (e.g., antisense) polynucleotide (suitable examples of which can be identified through standard gene walking procedures), which preferably facilitates one of the above-mentioned biological activities through inhibition of a biological activity inhibitor, examples of which are discussed further elsewhere herein. Polynucleotides, either encoding the ARFs of the invention or administered therewith, can take the form of aptamers (as described in, e.g., Famulok and Mayer - [http://www.chemie.uni-bonn.de/oc/ak\\_fa/publications/CTMI-paper.pdf](http://www.chemie.uni-bonn.de/oc/ak_fa/publications/CTMI-paper.pdf)), capable of binding to suitable targets. Triplex-forming inhibitory nucleotides also can be co-administered with the ARF-encoding polynucleotide, as can "decoys" comprising DNA binding domains specific for particular genes which are sought to be silenced but which encode a different factor.

[0156] Examples of suitable angiogenic factors that can be expressed (produced) with the fusion proteins of the invention (and, as such, can be encoded by the second nucleotide sequence) include, but are not limited to, fibroblast growth factors (FGFs) (e.g., aFGF (FGF-1) (also known as heparin binding factor 1), bFGF (FGF-2), HST, *int-2*, FGF-4, FGF-5, FGF-6, and KGF (as discussed in, e.g., Basilico and Moscatelli, "The FGF Family of Growth Factors and Oncogenes" in *ADVANCES IN CANCER RESEARCH*, 59, 115-65 (Woude and Klien eds., Academic Press 1992) and U.S. Patent 5,614,496) and their relatives (e.g., HDGFs, as described in, e.g., Klagsbrun et al., *Proc. Natl. Acad. Sci. USA*, 83, 2448 (1986)), angiogenins (e.g., angiogenin, angiogenin-2, and mAngiogenin-3, as described in, e.g., Strydom et al., *Biochemistry*, 24, 5486 (1985), Folkman et al., *Science*, 235, 442 (1987), Bond et al., *Biochim. Biophys. Acta*, 1162, 177 (1993), Hu et al., *Biochem. Biophys. Res. Commun.*, 197, 682. (1993), Hu et al., *Proc. Natl. Acad. Sci. USA*, 91, 12096 (1994), and Moenner et al., *Eur. J. Biochem.*, 226, 483 (1994)), pleiotrophin (PTN, also known as HBNF, HB-GAM, HBBM, p18, OSF-1, and HARP, among others, as described in, e.g., Kretschmer et al., *Growth Factors*, 5, 99 (1991), Kretschmer et al., *Biochem. Biophys. Res. Commun.*, 192(2), 420-29 (1993), U.S. Patent 5,270,449, European Patent 0 441 763, and European Patent Application 0 474 979), midkine (MK) (as described in, e.g., Böhlen and Kovesdi, *Prog. Growth Factor Res.*, 3, 143-57 (1991), Inui et al., *J. Peptide Sci.*, 2, 28-39 (1996), Iwasaki et al., *EMBO J.*, 16, 6936-46 (1997), and U.S. Patent 5,210,026), transforming growth factors (TGFs - e.g., TGF- $\beta$ ), gelatinases (as described in, e.g., Nguyen

et al., *Int. J. Biochem. Cell. Biol.* 33(10), 960-970 (2001)), placental growth factors, Kallistatins (as described in, e.g., Chao et al., *Biol. Chem.*, 382(1), 15-21 (2001), platelet-derived growth factors (e.g., platelet-derived endothelial cell growth factor and PDGF-BB (Regranex)), aniomotins (as described in, e.g., Troyanovsky et al., *J. Cell Biol.*, 152(6), 1247-54 (2001)), ECGF (as described in, e.g., U.S. Patent 4,868,113), cyclooxygenases (as described in, e.g., Dempke et al., *J. Cancer Res. Clin. Oncol.*, 127(7), 411-7 (2001)), Del-1 (as described in, e.g., U.S. Patents 5,877,281 and 5,874,562), erythropoietin, follistatin, granulocyte colony-stimulating factor (G-CSF), GM-CSF, scatter factor/hepatocyte growth factor (HGF) (as described in, e.g., U.S. Patents 6,011,009 and 6,133,231), leptin, insulin like growth factors (IGFs, e.g., IGF-I and IGF-II), ORP150 (as described in, e.g., Ozawa et al., *J. Clin. Invest.*, 108(1), 41-50 (2001)), endothelial growth factors (EGFs) (e.g., endothelial cell-derived growth factor (ECDGF) and PD-ECGF (as described in, e.g., Matsukawa et al., *Biochim. Biophys. Acta*, 1314(1-2), 71-82 (1996), Moghaddam et al., *Biochemistry*, 31, 12141-46 (1992), Miyazono et al., *Biochemistry*, 28, 1704-10 (1989), and Ishikawa, *Nature*, 338(6216), 557-62 (1989)), PP60 (C-Src) (as described in, e.g., Marx et al., *Exp. Mol. Pathol.*, 70(3), 201-13 (2001)), HBEGFs (as described in, e.g., U.S. Patent 6,037,329), epidermal growth factors, connective tissue growth factors (CTGFs - as described in, e.g., U.S. Patent 6,149,916 and Moussad et al., *Mol. Genet. Metab.*, 71(1-2), 276-92 (2000), preferably CTGF-2), gangliosides (as described in, e.g., Lang et al., *Biochem. Biophys. Res. Common.*, 282(4), 1031-37 (2001)), matrix metalloproteinases (MMPs) (as described in, e.g., Murphy et al., *Matrix Biol.*, 15(8-9), 511-8 (1997), Baramova et al., *Cell Biol. Int.*, 19(3), 239-42 (1995), and Matrisian, *Ann. N.Y. Acad. Sci.*, 732, 42-50 (1994)), tissue inhibitors of metalloproteinase (TIMPs, e.g., vasosten or TIMP-4) (as described in, e.g., Vallamo et al., *Human Pathol.*, 30(7), 795-802 (1999) and Dollery et al., *Circ. Res.*, 84(5), 498-504 (1999)), Survivins, Stat-3 (as described in, e.g., Yamauchi-Takahara et al., *Trends Cardiovasc. Med.*, 10(7), 298-303 (2000)), Delta-3 (as described in, e.g., U.S. Patent 6,121,045), COUP-TFII, eNOS, iNOS, MCP-1, proliferin, syndecan-4 proteins (as described in, e.g., International Patent Application WO 01/45751), RAF and RAS protein kinases (as described in, e.g., International Patent Application WO 01/12210), E-selectin, platelet-activating factors (PAFs) VCAM1, COX-2, HIV-tat, ephrins (e.g., EphB1, EphB2, or EphB4) (as described in, e.g., Yancopoulos et al., *Cell*, 93, 661-64 (1998) and references cited therein), TWEAK (as described in, e.g., Lynch et al., *J. Biol. Chem.*, 273(13), 8455-49 (1999)), CYR 61 (as described in, e.g., Babic et al., *Proc. Natl. Acad. Sci. USA*, 95, 6355 (1998)), VEGF-activating zinc finger protein (ZFP) transcription factors (as described in, e.g., International Patent Application WO 01/19981) Fibrin fragment E, PR39 (as described in, e.g., Li et al., *Nat. Med.*, 6(1), 49-55 (2000), and modified by *Nat. Med.*, 6(3), 356 (2000)), Mek3 (as described in, e.g., Yang et al., *Nat. Genet.*, 24(3), 309-13 (2000),

MEF2C (as described in, e.g., Bi et al., *Dev. Biol.*, 211(2), 255-67 (1999), prostacyclins (such as PGI<sub>2</sub> described in e.g., Spisniet et al., *Exp. Cell Res.*, 266(1), 31-43 (2001)), SDF-1 (as described in, e.g., Moore et al., *Ann. N.Y. Acad. Sci.*, 938, 36-47 (2001)) progestins (as described in e.g., U.S. Patent 6,245,757) tissue plasminogen activator (tPA), urokinase-plasminogen activator (uPA), coagulation/clotting factors (e.g., tissue factor, plasma coagulation factor VIIa (FVIIa), cofactor FVa, Factor X (Xa), thrombin (prothrombin), and fibrinogen, as discussed in, e.g., Carmeliet, *Science*, 293, 1602-1604 (2001) and references cited therein), caveolin-1 and caveolin-1-modifying agents (e.g., agonists) (as described in, e.g., European Patent Application 1 076 091), nicotine (as described in, e.g., International Patent Application WO 01/08684), angiogenic C-x-C chemokines (as described in, e.g., Colville-Nash et al., *Mol. Med. Today*, 13-23 (1997)), other angiogenic factors described in International Patent Applications WO 01/05825 and WO 01/32926, and the AHRs (as described in U.S. Patent 6,121,236). Other angiogenic peptides include cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-3 (IL-3), interleukin-18 (IL-18), and interleukin-8 (IL-8), and transcription factors such as HIF-1 (or HIF-1 $\alpha$  and/or HIF-2 $\alpha$ ), chimeric HIF factors (e.g., the HIF-1 $\alpha$ /VP16 factor described in Vincent et al., *Circulation*, 102, 2255-61 (2000)), homologs thereof (e.g., EPAS as described in, e.g., Maemura et al., *J. Biol. Chem.*, 274(44), 3165-70 (1999)), fragments thereof, or heterodimers thereof (e.g., a HIF-1 $\alpha$ /HIF-2 $\alpha$  heterodimer). Preferably, the angiogenic factor produced by expression with the fusion protein is an angiogenic factor that functions in a manner other than as a transcription factor. Desirably, the second nucleic acid sequence encodes an angiogenic VEGF or VEGF homolog, most desirably a non-heparin-binding VEGF (e.g., human VEGF<sub>121</sub>), such as those VEGF and VEGF homologs described in U.S. Patent Application 09/832,355, and references cited therein. Other preferred angiogenic mediators include HBNFs, MKs, aFGFs, and Del-1. Non-peptide angiogenic mediators that can be associated with the fusion protein or co-administered therewith include hormones such as oestrogens and proliferin, alcohols such as glycerol, pyridine derivatives (e.g., nicotinamide), and oligosaccharides such as hyaluronan.

[0157] If the polynucleotide encodes multiple gene products, a combination of expression control sequences (e.g., promoters) can be used, preferably which correspond to a pre-planned pattern of activity with the desired pattern and level of expression of the encoded factors. Thus, nucleotide sequences in the polynucleotide can be under the control of separate promoters having different expression profiles, e.g., at least one nucleic acid sequence is operably linked to an RSV promoter and at least one other nucleic acid sequence is operably linked to a CMV promoter. Alternatively, a hybrid promoter can be constructed which combines the desirable aspects of multiple promoters. For example, a CMV-RSV hybrid promoter combining the CMV promoter's initial rush of activity with the



RSV promoter's high maintenance level of activity is especially preferred for use in many embodiments of the inventive method. Thus, the invention provides polynucleotides where the fusion protein sequence is operably linked to a first promoter and a second nucleotide sequence is operably linked to a second promoter, such that the initiation of expression of the first nucleotide sequence and second nucleotide occurs at different times, in response to different factors, or both. Preferably, such promoter systems are designed to mimic expression patterns associated with normal biological activities, e.g., pathways or cascades. For example, a first promoter can drive the early expression (or separately inducible expression) of a vascular endothelial growth factor (VEGF) (e.g., human VEGF<sub>121</sub>, VEGF<sub>165</sub>, or VEGF<sub>189</sub>), and a second promoter can be later induced or otherwise later cause expression of a nucleic acid sequence encoding an ARF fusion protein of the invention.

[0158] The polynucleotide can include multiple fusion protein genes and/or related genes to be serially expressed and/or co-expressed. Thus, for example, the invention contemplates administration of polynucleotides that encode at least 3, at least 4, at least 5, or more, fusion protein genes or combinations of fusion protein genes, and other angiogenic factor genes, bone growth promoting factor genes, or wound healing promoting factor genes, which preferably mimic an expression pattern of a normal biological cascade. Suitable bone growth, wound healing, and angiogenic factors are described in U.S. Patent Application 09/832,355, and references cited therein. For example, the polynucleotide can include sequences encoding (1) a matrix metalloproteinase or other factor that promotes matrix degradation, (2) a VEGF or VEGF homolog (which preferably attracts endothelial cells and induces blood vessel formation), (3) a fusion protein of the invention, which preferably induces vascular maturation and/or reduces plasma leakage in the VEGF-induced vessels, and (4) an ephrin (which preferably induces stabilization and maintenance of the blood vessel), which are preferably operably linked to promoters such that they are expressed in a manner that mimics the normal biological cascade in blood vessel development in the host. Alternatively or additionally, multiple polynucleotides (e.g., within multiple vectors) can be administered, wherein the polynucleotides encode one or multiple genes, including at least one polynucleotide encoding one of the ARF fusion proteins of the invention, to provide such a cascade effect. However, the administration of a single polynucleotide under control of the above-described expression control sequence systems is preferred.

[0159] Production of the recombinant polynucleotide encoding the fusion protein can be accomplished by any suitable technique. Recombinant polynucleotide production is well understood, and methods of producing such molecules are provided in, e.g., Mulligan, *Science* 260, 926-932 (1993), Friedman, *Therapy For Genetic Diseases* (Oxford University Press, 1991), Ibanez et al., *EMBO J.*, 10, 2105-10 (1991), Ibanez et al., *Cell*, 69, 329-41

(1992), and U.S. Patents 4,440,859, 4,530,901, 4,582,800, 4,677,063, 4,678,751, 4,704,362, 4,710,463, 4,757,006, 4,766,075, and 4,810,648, and are more particularly described in Sambrook and Ausubel, *supra*.

**[0160]** The polynucleotide preferably is positioned in and/or administered in the form of a suitable delivery vehicle (i.e., a vector). The vector can be any suitable vector. For example, the nucleic acid can be administered as a naked DNA or RNA vector, including, for example, a linear expression element (as described in, e.g., Sykes and Johnston, *Nat. Biotech.*, 17, 355-59 (1997)), a compacted nucleic acid vector (as described in, e.g., U.S. Patent 6,077,835 and/or International Patent Application WO 00/70087), a plasmid vector such as pBR322, pUC 19/18, or pUC 118/119, a "midge" minimal-sized vector (as described in, e.g., Schakowski et al., *Mol. Ther.*, 3, 793-800 (2001)) or as a precipitated nucleic acid vector construct (e.g., a CaPO<sub>4</sub> precipitated construct). The vector also can be a shuttle vector, able to replicate and/or be expressed (desirably both) in both eukaryotic and prokaryotic hosts (e.g., a vector comprising an origin of replication recognized in both eukaryotes and prokaryotes). The nucleic acid vectors of the invention can be associated with salts, carriers (e.g., PEG), formulations which aid in transfection (e.g., sodium phosphate salts, Dextran carriers, iron oxide carriers, or gold bead carriers), and/or other pharmaceutically acceptable carriers, some of which are described herein. Alternatively or additionally, the polynucleotide vector can be associated with one or more transfection-facilitating molecules such as a liposome (preferably a cationic liposome), a transfection facilitating peptide or protein-complex (e.g., a poly(ethylenimine), polylysine, or viral protein-nucleic acid complex), a virosome, a modified cell or cell-like structure (e.g., a fusion cell), or a viral vector. The polynucleotide also can be administered with a vector which catalyzes disulfide bond formation (as described in, e.g., International Patent Application WO 98/37208).

**[0161]** More preferably, the polynucleotide is positioned in, and administered to the host via, a viral vector. The viral vector can be any suitable viral vector. A viral vector in the context of the invention includes any combination of nucleotides and proteins that are derived from, obtained from, or based upon proteins and or nucleic acids that are present in a wild-type virus. For example, the viral vector can comprise a virus-like particle (VLP) or a vector similar to those described in U.S. Patent 5,849,586 and International Patent Application WO 97/04748. The viral vector can be a vector which requires the presence of another vector or wild-type virus for replication and/or expression (i.e., a helper-dependent virus), such as an adenoviral vector amplicon. The viral vector preferably consists of an intact virus particle. Typically, such viral vectors consist essentially of a wild-type viral particle, or a viral particle modified in its protein and/or nucleic acid content to increase transgene capacity or aid in transfection and/or expression of the nucleic acid (examples of

such vectors include the herpes virus/AAV amplicons). Such vectors are typically named for the type of virus they are obtained from, derived from, or based upon, as applicable. Examples of preferred viral vectors include herpes viral vectors, adeno-associated viral vectors, and adenoviral vectors. Suitable examples of such vectors and other suitable viral vectors are provided in, e.g., Mackett et al., *J. Gen. Virol.*, 67, 2067-82 (1986), Beaud et al., *Dev. Biol. Stand.*, 66, 49-54 (1987), Levine, *Microbiol. Sci.*, 4(8), 245-50 (1987), Lebowski et al., *Mol. Cell Biol.*, 8(10), 3988-96 (1988), Nicholas et al., *Biotechnology*, 10, 493-513 (1988), Moss et al., *Curr. Top. Microbiol. Immunol.*, 158, 25-38 (1992), Berihoud et al., *Curr. Opin. Biotechnol.*, 10(5), 440-47 (1999), Yonemitsu, *Nat. Biotechnol.*, 18(9), 970-3 (2000), and Russell, *J. Gen. Virol.*, 81, 2573-2604 (2000), as well as International Patent Application WO 00/32754. Desirably, the viral vector particle is a mammalian viral vector, a non-enveloped viral vector, and a vector that contains a DNA-based genome.

[0162] The construction of recombinant viral vectors is well understood in the art. For example, adenoviral vectors can be constructed and/or purified using the methods set forth, for example, in Graham et al., *Mol. Biotechnol.*, 33(3), 207-220 (1995), U.S. Patents 5,922,576, 5,965,358 and 6,168,941 and International Patent Applications WO 98/22588, WO 98/56937, WO 99/15686, WO 99/54441, and WO 00/32754. Adeno-associated viral vectors can be constructed and/or purified using the methods set forth, for example, in U.S. Patent 4,797,368 and Laughlin et al., *Gene*, 23, 65-73 (1983). Similar techniques are known in the art with respect to other viral vectors, particularly with respect to herpes viral vectors (see e.g., Lachman et al., *Curr. Opin. Mol. Ther.*, 1(5), 622-32 (1999)), lentiviral vectors, and other retroviral vectors.

[0163] The viral vector can be a chimeric viral vector. Examples of suitable chimeric viral vectors are described in, e.g., Reynolds et al., *Mol. Med. Today*, 5(1), 25-31 (1999) and Bournsnel et al., *Gene*, 13, 311-317 (1991).

[0164] Desirably, the viral vector is capable of expressing the polynucleotide for a sustained period (e.g., for a period of at least about 1 day, preferably about 1 week), without expressing the polynucleotide so long that undesired effects associated with prolonged expression, e.g., promiscuous angiogenesis, occurs (e.g., for a period of less than about 2 weeks). Thus, the viral vector preferably is capable of therapeutic, and transient, self-terminating expression of the polynucleotide (e.g., expression for a period of about 1 week or less). Preferably, the viral vector achieves gene transfer in both dividing and non-dividing, as well as terminally differentiated, cells, with high levels of expression in cardiovascular relevant sites such as the myocardium, vascular endothelium, and skeletal muscle. The viral vector desirably is safe for administration to the host. Advantageously, the viral vector operates in an episomal manner without insertion of genetic material to the host. Adenoviral vectors, which possess all of these aforementioned qualities, are

particularly preferred delivery vectors for nucleic acid angiogenic mediators.

**[0165]** Any suitable adenoviral vector can be used as a delivery vehicle for the polynucleotide. For instance, an adenovirus can be of subgroup A (e.g., serotypes 12, 18, and 31), subgroup B (e.g., serotypes 3, 7, 11, 14, 16, 21, 34, and 35), subgroup C (e.g., serotypes 1, 2, 5, and 6), subgroup D (e.g., serotypes 8, 9, 10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, and 42-47), subgroup E (serotype 4), subgroup F (serotypes 40 and 41), or any other adenoviral serotype. Preferably, the adenoviral vector is based on, derived from, or consists of a serotype-2 or serotype-5 adenovirus. In some aspects, type 35 adenoviral vectors (as described in, e.g., International Patent Application WO 01/41814) can be advantageous, particularly where immune response to the vector is a concern.

**[0166]** Regions of the adenoviral genome (e.g., the E3 region) in the adenoviral vector can optionally and preferably will be deleted in order to provide space for insertion of the polynucleotide or other nucleic acid sequences. In addition, regions of the adenoviral genome can be deleted or altered in order to interfere with viral replication. The adenoviral vector used in the inventive method preferably is deficient in at least one gene function required for viral replication, thereby resulting in a "replication-deficient" adenoviral vector. Preferably the adenoviral vector will be deficient in at least one essential gene function of the E1, E2, and/or E4 regions of the adenoviral genome. More preferably, the adenoviral vector is deficient in at least one essential gene function of the E1 region (e.g., deficient in at least part of the E1a region and/or at least part of the E1b region) of the adenoviral genome. Other portions of the genome also can be deleted, e.g., typically the E3 region, which is non-essential for viral replication. Thus, the adenoviral vector can be lacking multiple adenoviral gene functions, e.g., at least one essential gene function of the E1 region and at least one essential gene function of the E4 region, in addition to at least part of the E3 region. Examples of E1-deleted and other replication deficient adenoviral vectors are disclosed in, for example, U.S. Patents 5,851,806, 5,985,655, and 5,994,106 and International Patent Applications WO 95/34671 and WO 97/21826. The adenoviral vector desirably retains at least one adenovirus inverted terminal repeat (ITR) (preferably the 5' and 3' ITRs). The adenoviral vector also desirably retains the adenovirus packaging sequence. Preferably, the recombinant adenovirus also comprises a mutation in the major late promoter (MLP), as discussed in International Patent Application WO 00/00628. Alternatively or additionally, the adenoviral vector can retain an E3-gp19K coding sequence, particularly where immune response to the adenoviral vector is a concern.

**[0167]** The vector, including the viral vector, can integrate into the host cell's genome or be a non-integrative vector. Non-integrative vectors, e.g., naked DNA plasmids, and particularly non-integrative viral vectors (e.g., adenoviral vectors), are typically preferred. Alternatively, a lentiviral vector, naked DNA vector comprising integration-promoting

sequences (as described in, e.g., International Patent Applications WO 98/41645 and WO 98/54345), or AAV viral vector that integrates into the host cell's genome can be used. Additionally, when using a non-integrating viral vector, control sequences that allow for retention of the delivered transgene in the host cell, either by integration into the target cell genome or by maintenance as an episomal nucleic acid can be utilized (as discussed in, e.g., International Patent Application WO 98/54345).

**[0168]** A particularly preferred adenoviral vector for use in the inventive method is deficient in the entire E1a region, at least part of the E1b region, and at least part of the E3 region of the adenoviral genome and contains a DNA encoding a fusion protein comprising an Ang-1, KAP, or angiopoietin-like FLD directly fused to a sequence encoding a NL1, NL5, or Ang-2X CCD, under the control of the CMV IE promoter in the E1 region of the adenoviral genome. Such a vector supports *in vivo* production of the fusion protein that is maximized at one day following administration and is not detectable above baseline levels as little as one week after administration.

**[0169]** The adenoviral vector can be subject to any number of additional or alternative modifications. For example, a particularly preferred vector comprises a replication-deficient adenoviral vector which includes or produces (by expression) a modified adenoviral protein, non-adenoviral protein, or both, which increases the efficiency that the vector infects cells as compared to wild-type adenovirus, allows the vector to infect cells which are not normally infected by wild-type adenovirus, results in a reduced host immune response in a mammalian host as compared to wild-type adenovirus, or any combination thereof. Any suitable type of modification can be made to the vector, and several suitable modifications are known in the art. For example, the adenoviral vector coat protein can be modified. Examples of such modifications include modifying the adenoviral fiber, penton, pIX, pIIIa, or hexon proteins, and/or insertions of various native or non-native ligands into portions of such coat proteins. Manipulation of such coat proteins can broaden the range of cells infected by a viral vector or enable targeting of a viral vector to a specific cell type. One direct result of manipulation of the viral coat is that the adenovirus can bind to and enter a broader range of eukaryotic cells than a wild-type virus. Examples of adenoviruses including such modifications are described in International Patent Application WO 97/20051. Reduction of immune response against the adenoviral also or alternatively can be obtained through the methods described in U.S. Patents 6,093,699 and 6,211,160 and/or U.S. Patent Application 2001-0006947A1. In other embodiments, the viral coat is manipulated such that the virus is "targeted" to a particular cell type, e.g., those cells expressing unique receptors. Examples of such modified adenoviral vectors are described in Miller et al., *FASEB J.*, 9, 190-99 (1995), Douglas et al., *Nat. Biotechnol.*, 14(11), 1574-78 (1996), Wickham, *Gene Ther.*, 7(2), 110-14 (2000), U.S. Patents 5,559,099, 5,731,190,

5,712,136, 5,770,442, 5,846,782, 5,962,311, 5,965,541, 5,985,655, 6,030,954, 6,057,155 and International Patent Applications WO 96/07734, WO 96/26281, WO 97/20051, WO 98/07865, WO 98/07877, WO 98/40509, WO 98/54346, WO 00/15823 and WO 00/31285. Other adenoviral vector protein modifications that decrease the potential for immunological recognition by the host and resultant coat-protein directed neutralizing antibody production, as described in, e.g., International Patent Applications WO 98/40509 and WO 00/34496. In non-viral vector systems, the use of targeting through targeted proteins (e.g., an asialoorosomucoide protein conjugate which promotes liver targeting (such as is described in Wu and Wu, *J. Biol. Chem.*, 263 (29), 14621-24 (1988)) or the targeted cationic lipid compositions of U.S. Patent 6,120,799).

[0170] The adenoviral vector also can include a *trans*-acting factor, *cis*-acting factor, or both, which preferably increases the persistence of transgene expression from the adenoviral vector's genome. Any suitable *trans*-acting factor can be used, such as HSV ICP0, which prolongs transgene expression (e.g., expression of the fusion protein sequence). Such modifications are particularly preferred in E4-deleted adenoviral vectors. The use of *trans*-acting factors is further described in International Patent Application WO 00/34496.

Additionally or alternatively, the adenoviral vector comprises a nucleic acid sequence encoding a *cis*-acting factor. For example, a matrix attachment region (MAR) sequence (e.g., an immunoglobulin heavy chain  $\mu$  (as discussed in, e.g., Jenuwein et al., *Nature*, 385(16), 269 (1997)), locus control region (LCR) sequences, or apolipoprotein B sequence (as discussed in, e.g., Kalos et al., *Molec. Cell. Biol.*, 15(1) 198-207 (1995)) can be used to modify the persistence of expression from a transgene, such as a transgene inserted into an E4-deleted region of the adenoviral vector genome. LCR sequences are also believed to establish and/or maintain transcription of transgenes in a *cis* manner.

[0171] The polynucleotide can be positioned within any suitable location in the genome of the adenoviral vector. Typically, the polynucleotide will substitute for one or more of the aforementioned deleted regions of the adenoviral genome (e.g., the E1, E2, E3, and/or E4 region, most preferably replacing at least a portion of the E1 region). Alternatively, several polynucleotides encoding multiple fusion proteins, or fusion proteins and other proteins (e.g., a second angiogenic, bone growth promoting, or wound healing promoting peptide-encoding sequence) can be inserted as expression cassettes into multiple deleted regions (e.g., the ARF fusion protein encoding sequence can be inserted in a portion of the E1 region, and the polynucleotide encoding the second factor (e.g., a VEGF<sub>121</sub> gene) can be inserted in the deleted E3 region, or vice versa).

[0172] Production of such deficient adenoviral vectors can be accomplished by use of a complementation cell line, which is capable of providing the deleted necessary adenoviral gene functions *in trans*. Several examples of suitable cells are known. Examples of

suitable cells for producing such vectors include 293 cells (described in, e.g., Graham et al., *J. Gen. Virol.*, 36, 59-72 (1977)), HER cells, such as 911 cells (as described in, e.g., Fallaux et al., *Human Gene Therapy*, 7, 215-222 (1996)) or PER.C6 cells (commercially available through Crucell (Leiden, Netherlands)), and 293-ORF6 cells (as described in, e.g., International Patent Application WO 95/34671 and Brough et al., *J. Virol.*, 71, 9206-13 (1997)). The cell line can provide either no homologous overlapping regions with the adenoviral vector, ideally resulting in no replication competent adenovirus (RCA) or, alternatively, can partially overlap in one or more essential regions but lack homology in one or more essential regions (as exemplified by the cells in International Patent Application WO 95/34671). Desirably, the vector composition of the invention is formed from a purified stock of such vectors. A preferred method for purifying such vector stocks is provided in International Patent Application WO 99/54441. Methods for assessing the purity of such vector compositions are provided in International Patent Application WO 00/12765.

**[0173]** The polynucleotide encoding the fusion protein can be inserted in any of the above-described vectors in any suitable manner and in any suitable orientation. Whereas the polynucleotide can be inserted in any suitable orientation, preferably the orientation of the nucleic acid is from right to left. By the polynucleotide having an orientation "from right to left," it is meant that the direction of transcription of the nucleic acid is opposite that of the region of the vector into which the polynucleotide is inserted.

**[0174]** The invention further provides methods of administering the fusion proteins, polynucleotides, and vectors of the invention to a cell, tissue, or host (preferably a human), to modulate, preferably to promote angiogenesis. Thus, for example, the invention provides a method of promoting angiogenesis in an individual comprising administering to the individual an amount of a fusion protein that is effective to promote angiogenesis. Administration of the fusion protein can be performed by any suitable method, and the fusion protein can be administered in any suitable form (including by way of the polynucleotide or vector described herein). Preferably, the fusion protein (or polynucleotide or vector encoding the fusion protein) is administered in a composition, with a carrier, preferably in a pharmaceutically acceptable composition, e.g., by combination with a pharmaceutically acceptable carrier.

**[0175]** The term "pharmaceutically acceptable" means that the composition is a non-toxic material that does not interfere with the effectiveness of the biological activity of the fusion protein or other effective ingredients. Any suitable carrier can be used, and several carriers for administration of therapeutic proteins are known in the art. The characteristics of the carrier will depend on the route of administration.

**[0176]** The pharmaceutical composition and/or pharmaceutically acceptable carrier also

can include diluents, fillers, salts (preferably monovalent salts in a concentration of about 100-200 mM), buffers (preferably which retain a pH at about 7-8.5 at room temperature for vector compositions), detergents (preferably nonionic detergents, such as Tween-80), stabilizers, solubilizers, and/or other materials suitable for inclusion in a pharmaceutically composition. The pharmaceutical composition of the invention also can contain preservatives, antioxidants, or other additives known to those of skill in the art. When the fusion protein (or polynucleotide or vector encoding is fusion protein) is administered with other agents or ingredients the combined amounts of the agents can be administered in combination, serially or simultaneously. Examples of suitable components of the pharmaceutical composition in this respect are described in, e.g., Berge et al., *J. Pharm. Sci.*, 66(1), 1-19 (1977), Wang and Hanson, *J. Parenteral. Sci. Tech.*, 42, S4-S6 (1988), U.S. Patents 6,165,779 and 6,225,289, and elsewhere herein.

[0177] The pharmaceutical composition of the invention can be in the form of a liposome in which the fusion protein (or polynucleotide or vector encoding the fusion protein) is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is described in, e.g., U.S. Patents 4,837,028 and 4,737,323.

[0178] The pharmaceutical composition can be delivered to the individual by any suitable route of administration. Examples of suitable routes of administration include oral ingestion, inhalation, bucal application, rectal application, vaginal application, topical application, insufflation, implantation, transmucosal administration, or cutaneous, subcutaneous, intraperitoneal, parenteral, myocardial, pericardial (e.g., intrapericardial), or injection (e.g., intravenous injection). Intravenous administration and injection are preferred.

[0179] If the pharmaceutical composition is administered orally, the composition preferably is administered in the form of a tablet, capsule, powder, solution, elixir, or troches. Oral compositions can include any suitable carriers or other agents. For example, tablets will typically contain a solid carrier, such as a gelatin. Generally, oral compositions also can include binders (e.g., microcrystalline cellulose, gum tragacanth or gelatin), excipients (e.g., starch or lactose), disintegrating agents (e.g., alginic acid, Primogel, or corn starch), lubricants (e.g., magnesium stearate or Sterotes), glidants (e.g., colloidal silicon dioxide), and/or sweetening/flavoring agents. Oral compositions preferably contain about 5-95%, preferably about 25-90%, fusion protein (or polynucleotide or vector encoding the fusion protein).



**[0180]** To administer the fusion protein (or polynucleotide or vector encoding the fusion protein) in a liquid form, such as in delivery by injection, a liquid carrier such as water, petroleum, physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ), phosphate buffered saline (PBS), or oils can be used as a carrier. Liquid pharmaceutical compositions can further contain physiological saline solution, dextrose (or other saccharide solution), polyols, or glycols, such as ethylene glycol, propylene glycol, PEG, coating agents which promote proper fluidity, such as lecithin, isotonic agents, such as mannitol or sorbitol, organic esters such as ethyloleate, and absorption-delaying agents, such as aluminum monostearate and gelatins. When administered in liquid form, the pharmaceutical composition preferably contains about 0.5-90% by weight (wt.%) of fusion protein (or polynucleotide or vector encoding the fusion protein), more preferably about 1-50 wt.% fusion protein (or polynucleotide or vector encoding the fusion protein).

**[0181]** More particularly, when the pharmaceutical composition is administered by injection, the composition will preferably be in the form of a pyrogen-free, stable, parenterally acceptable aqueous solution. Preferably, the parenterally acceptable aqueous solution comprises an isotonic vehicle such as sodium chloride injection, Ringer's injection, dextrose injection, lactated Ringer's injection, or equivalent delivery vehicle (e.g., sodium chloride/dextrose injection).

**[0182]** In a particularly preferred aspect, the fusion protein polynucleotide, or vector is administered in or near the heart. Administration in or near the heart can be to any suitable heart-associated region or tissue, using any suitable technique. Examples of suitable types of administration include direct (needle or biolistic) intracoronary injection (e.g., of a vector composition) and/or intracoronary administration using implant devices (e.g., a fusion protein coated coronary stent). Pericardial, myocardial, and intracoronary administration are particularly preferred for angiogenic fusion proteins used to treat vascular occlusion in an individual's heart.

**[0183]** The fusion protein (and polynucleotide or vector, as applicable) can be desirably co-administered with another factor, preferably a factor that promotes angiogenesis, bone growth, or wound healing (most preferably angiogenesis). Where the fusion protein, polynucleotide, or vector is administered with a wound healing or bone growth-promoting factor, preferred methods of administration (e.g., topical administration systems, implants, and specialized compositions) preferably will be one set forth in U.S. Patent Application 09/832,355 and references cited therein. The second factor can be a separate protein, or a vector or polynucleotide that produces such a protein.

**[0184]** Preferably, the second factor is a non-heparin-binding VEGF, a polynucleotide comprising a nucleic acid sequence encoding a non-heparin-binding VEGF, or a vector comprising a polynucleotide encoding a non-heparin-binding VEGF. As discussed above,

the fusion protein also can comprise non-ARF peptide portions that assist in promoting angiogenesis or other desired biological activities. Furthermore, the polynucleotide of the invention can comprise one or more nucleic acid sequences encoding additional factors that promote angiogenesis or other desired biological activity as well as the fusion protein of the invention.

[0185] Administration devices for the fusion protein, polynucleotide, or vector can be formed of any suitable material. Examples of suitable matrix materials for producing non-biodegradable administration devices include hydroxapatite, bioglass, aluminates, or other ceramics. In some applications, a sequestering agent, such as carboxymethylcellulose (CMC), methylcellulose, hydroxypropylmethylcellulose (HPMC), or autologous blood clot, can be used to prevent the fusion protein complex from disassociating from the device and/or matrix. Thus, such sequestering agents are preferably present in an amount which prevents desorption of the fusion protein from the matrix/device and/or provides better handling of the composition. Typically, such sequestering agents will make up about 0.5-20 wt.%, preferably about 1-10 wt.%, of the composition, based on total formulation weight.

[0186] For administration by inhalation, the fusion protein (or polynucleotide or vector encoding the fusion protein) can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e. g., a gas such as carbon dioxide, or a nebulizer.

[0187] For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are preferably included in the composition. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be facilitated through the use of nasal sprays or suppositories.

[0188] The invention further provides compositions comprising the fusion protein (or polynucleotide or vector encoding the fusion protein) for the preparation of pharmaceuticals or other medicaments, e.g., for the preparation of sterile injectable solutions (desirably any of the other compositions described herein also are sterile). Such powder compositions can be prepared by, e.g., vacuum drying and freeze-drying, which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The compositions of the invention also or alternatively can be provided in unit dose containers and devices, including ampoules, disposable syringes, or multiple dose vials.

[0189] Additional pharmaceutically acceptable carriers are known in the art. Examples of additional suitable carriers are described in, e.g., Urquhart et al., *Lancet*, 16, 367 (1980), Lieberman et al., PHARMACEUTICAL DOSAGE FORMS - DISPERSE SYSTEMS (2nd ed., vol. 3, 1998), Ansel et al., PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS (7th ed.

2000), REMINGTON'S PHARMACEUTICAL SCIENCES, and U.S. Patents 5,708,025 and 5,994,106.

**[0190]** The specific amount of fusion protein (or polynucleotide or vector encoding the fusion protein) in a dosage of the composition administered to the individual will depend upon the biological effect desired in the individual, condition to be treated, and/or the specific characteristics of the fusion protein (or polynucleotide or vector encoding the fusion protein) and individual. Preferably, the pharmaceutical composition is administered in a therapeutically effective amount. A "therapeutically effective amount" means an amount sufficient to show a meaningful benefit in an individual, i.e., promoting at least one aspect of angiogenesis other desired biological effect (e.g., receptor binding), or treatment, healing, prevention, or amelioration of other relevant medical condition(s). Therapeutically effective amounts may vary depending on factors such as those described above. Thus, the attending physician (or other medical professional responsible for administering the composition) will typically decide the amount of fusion protein with which to treat each individual patient. Generalized guidance in making such determinations can be found, for example, in Platt, *Clin. Lab Med.*, 7, 289-99 (1987), and in "Drug Dosage," *J. Kans. Med. Soc.*, 70(1), 30-32 (1969).

**[0191]** Proper dosage can be determined by any suitable technique. In a simple dosage testing technique, low doses of the composition are administered to a test subject or system (e.g., an animal model, cell-free system, or whole cell assay system). Larger doses of the composition then can be administered until the desired therapeutic effect is obtained. For example, Doppler imaging can be used to detect blood flow and/or microscopy can be used to detect changes in blood vessel number or quality. Preferably, the dosage is within a range that includes the ED<sub>50</sub>, with low average toxicity. Such dosages are expected to typically contain about 0.01 mg-100 mg, preferably about 0.1-10 mg, more preferably about 0.1-1 mg, of fusion protein per kg body weight. Dosages with respect to vectors containing polynucleotides encoding the fusion protein are described elsewhere herein; however, it should be understood that the discussion provided with respect to dosage and administration of the fusion protein and of such vectors are considered interchangeable unless explicitly stated otherwise or clearly contradicted by the text.

**[0192]** The invention further provides a method of producing the fusion protein by introducing a vector containing a polynucleotide, which, when expressed, results in the production of a fusion protein of the invention, into a suitable cell, such that the nucleotide sequence is expressed and the fusion protein is produced. The vector can be introduced into a suitable host cell for purpose of producing the fusion protein, which is then substantially isolated, preferably purified, which can be administered to an individual as described above. Any cell permissive for the uptake and maintenance of the vector and expression of the

polynucleotide can be suitable. Examples of suitable cells include bacterial cells, such as *E. coli* and mammalian cloned cells, such as HeLa cells, CHO cells, and VERO cells.

Transformation and/or transfection of such cells can be accomplished using techniques described herein or in Sambrook and Ausubel, *supra* and U.S. Patent 5,371,017. The fusion protein produced in the host cell can be identified and substantially isolated (preferably completely isolated) using standard techniques, including genetic selection, cell surface display, phage and virus display, ribosome display, fluorescence-based cell sorting, and agar plate screening (preferably combined with automated colony picking). Where fewer candidates need to be screened, more sensitive and faster techniques such as HPLC, mass spectrometry, gas chromatography, or chromogenic techniques can be applied.

[0193] The invention also provides a cell comprising a polynucleotide encoding any of the fusion proteins or other novel ARFs described herein. The cell can be any suitable cell, including any of the aforementioned cells or cells described elsewhere herein. The invention further provides in this respect a non-human transgenic animal comprising such a polynucleotide. The production of such transgenic animals are known in the art.

[0194] Alternatively, and preferably, such a vector is administered to an individual (e.g., a mammalian host, such as a human), resulting in the *in vivo* production of the fusion protein. *In vivo* administration of the fusion protein by way of such vectors offers several advantages over direct protein administration, including, e.g., avoidance of the first pass effect and other metabolically-related processing problems, providing intracellular production and processing, and providing sustained administration over a period of time, thereby resulting in less need for repeated administration events. The vector containing the fusion protein-encoding polynucleotide will preferably be administered to an area of the individual's body such that it promotes angiogenesis.

[0195] The vector is desirably administered near one or more angiogenically functional locations (source locations) and at least one angiogenically dysfunctional location (target location). Desirably, the vector (or fusion protein) composition is administered in a gradient forming manner, as described in International Patent Application WO 01/34179, particularly where the vector comprises a polynucleotide sequence comprising a second nucleic acid sequence encoding an angiogenic factor (e.g., a VEGF). The source location can be any location in the individual (e.g., tissue or organ), which has physiologically normal levels of blood perfusion, such as an area near or imbued with existing blood vessels (e.g., a non-ischemic area). The target location preferably is an actual or potentially angiogenically dysfunctional location, e.g., a location in the host that is either undergoing or is at risk of undergoing ischemia or any other condition wherein the growth of new, or extension of existing, blood vessels is desirable. Thus, the target location typically will be suffering from or be at risk of suffering from ischemic damage, which results when the

tissue is deprived of an adequate supply of oxygenated blood. The interruption of the supply of oxygenated blood is often caused by a vascular occlusion. Such vascular occlusion can be caused by arteriosclerosis, trauma, surgical procedures, disease, and/or other indications. There are many ways to determine if a tissue is at risk of suffering ischemic damage from undesirable vascular occlusion including, e.g., <sup>99m</sup>Tc-sestamibi scanning, x-ray imaging, Doppler imaging, and MRI scanning. The target location also can comprise a tissue in which blood flow is attenuated by trauma, surgery, or other events. The alleviation of such attenuated blood supply, regardless of its origin, is contemplated by the invention. Thus, prevention or alleviation of damage from indications such as myocardial ischemia (particularly in patients suffering from insulin dependent diabetes), delayed wound healing, Buerger's disease, and stroke are contemplated.

[0196] Additionally, the planning of a surgical procedure can be predictive of the interruption of blood supply through a particular portion of a patient's vasculature. Prior treatment according to the method of the invention can substantially improve the desired outcome of these surgeries. In that case, treatment preferably occurs about one day to about six weeks before the surgery, and more preferably about two to about fourteen days prior to surgery. Other prophylactic uses of the vector also are contemplated.

[0197] The target and source locations can be in any suitable tissue susceptible to new blood vessel growth upon production of a therapeutic amount of the angiogenic fusion protein. For example, the target and source locations can be located in a discrete organ such as the brain, heart, pancreas, limbs, or generalized areas of the body, such as a leg or a foot. Preferably, the target location and source location comprise portions of an organ system that includes at least two arteries (e.g., a heart which comprises at least three major arteries). In such aspects, the target location typically comprises at least a portion of an angiogenically dysfunctional artery in the system (e.g., an artery suffering from vascular occlusion), and some, if not all, of the angiogenically functional arteries in the system serve as source locations. In such aspects, the angiogenic mediator preferably is administered in a distribution between the target artery and the source arteries. Where the target location is an artery suffering from vascular occlusion, the method can comprise administration of the vector upstream, downstream, or to the occluded region of the artery (i.e., with respect to normal blood flow), or any combination thereof, as desired, preferably such that induced collateral blood vessel development bypasses the occluded region. "Tissue" in this sense is thus meant to include interstitial spaces associated with solid tissue. The source and target locations also can comprise cavities or extracellular fluid next to a tissue.

[0198] The polynucleotide or vector can be administered in the form of a composition, e.g., with or in any suitable acceptable carrier, preferably a pharmaceutically acceptable carrier, such as those described elsewhere herein. Additional pharmaceutically acceptable

carriers particularly suitable for administration of vectors are described in, for example, International Patent Application WO 98/32859.

**[0199]** The desired dosage (i.e., total dosage to the host) of the vector composition is such that the amount of fusion protein produced by expression of the polynucleotide in the vector results in a therapeutic and/or prophylactic effect in the area where the vector is administered. The dosage will depend on the type of fusion protein to be produced. Because a wide range of suitable fusion proteins are provided by the invention, dosage is described generally, augmented by examples relating to specific vector compositions. It will be understood that this type of description is meant to further illustrate the invention without limiting it to any particular vector composition.

**[0200]** The dosage of an adenoviral vector containing a fusion protein-encoding polynucleotide will be at least about  $1 \times 10^6$  particle forming units (pfu) (e.g.,  $1 \times 10^6$  -  $1 \times 10^{13}$  pfu) to an area near, at, or between the target and source locations. The dose preferably is at least about  $1 \times 10^7$  pfu (e.g., about  $1 \times 10^7$  -  $1 \times 10^{13}$  pfu), more preferably at least about  $1 \times 10^8$  pfu (e.g., about  $1 \times 10^8$  -  $1 \times 10^{11}$  pfu), and most preferably at least about  $1 \times 10^9$  pfu (e.g., about  $1 \times 10^9$  -  $1 \times 10^{10}$  pfu). The dose typically is for a volume of targeted tissue of about 0.5-15  $\text{cm}^3$ , but can be for larger tissue volumes of up to 100  $\text{cm}^3$  or even about 150  $\text{cm}^3$ . The dose desirably is administered via multiple applications and, as such, is divided among the multiple applications. Thus, if the dose is administered via 10 administrations, each administration involves about  $1 \times 10^5$  -  $1 \times 10^{12}$  pfu. Preferably, each application involves about  $1 \times 10^6$  -  $1 \times 10^{12}$  pfu, more preferably about  $1 \times 10^7$  -  $1 \times 10^{10}$  pfu, and most preferably about  $1 \times 10^8$  -  $1 \times 10^9$  pfu. For purposes of considering the dose in terms of particle units (pu), also referred to as viral particles, it can be assumed that there are 100 particles/pfu (e.g.,  $1 \times 10^{12}$  pfu is equivalent to  $1 \times 10^{14}$  pu). In a single round of vector administration, using, for example, an adenoviral vector deleted of the entire E1a region, part of the E1b region, and part of the E3 region of the adenoviral genome, wherein the vector comprises a nucleic acid encoding, e.g., an NL1 FLD/Ang-2X CCD fusion protein under the control of a standard CMV immediate early promoter, about  $10^7$ - $10^{13}$  pfu, preferably about  $10^9$ - $10^{11}$  pfu, are administered to the host (e.g., to a discrete organ containing the source and/or target locations) with an estimated volume of about 150  $\text{cm}^3$ . Under these conditions, a substantial level of fusion protein production is achieved in the tissue of interest without producing detectable levels of fusion protein production in distal tissues.

**[0201]** The vector composition can be administered to the individual by any suitable technique, including those techniques described herein with respect to fusion protein-containing compositions or polynucleotides and vectors. Preferably, the vector is injected into the individual. Injection can be performed in any suitable tissue or body part (e.g., intravenously, myocardially, parenterally, intrathecally, intradermally, intraspinally,

intraocularly, subdermally, or into the interstitial space of a tissue/organ (e.g., of a muscle tissue)). By the term "injecting," it is meant that the vector containing solution is forcefully introduced into the target tissue. The vector composition can be microinjected, injected directly by a needle, or injected by biolistic injection. Injection can be performed using any suitable device, such as the device described in U.S. Patent 5,846,225. Alternatively, the vector containing composition can be delivered by means of percutaneous administration, typically by use of a device, such as a catheter (e.g., inserted into the femoral artery) or by a stent coated with a suitable vector containing composition (e.g., which is placed in a suitable artery, such as a coronary artery).

[0202] The vector alternatively or additionally can be administered to any suitable surface, either internal or external, at or near the source and/or target locations. For example, with respect to directly injecting a vector containing a polynucleotide encoding an angiogenic fusion protein into cardiac tissue, it is contemplated that such an injection can be administered from any suitable surface of the heart (i.e., the angiogenic mediator can be administered endocardially, epicardially, and/or pericardially). Typically and preferably, cardiac administration will be to or in the left free ventricular wall of the heart that is easily accessible by minimally invasive thoracotomy. Alternatively, administration to other areas of the heart (e.g., the septum and/or right ventricle) can be accomplished by use of a catheter or other percutaneous delivery device. Such alternate techniques can be desired where the target location is positioned in the heart but away from the left free ventricular wall (e.g., where the target location is a vascular occlusion in the right coronary artery). For wounds at or near the skin surface, topical and/or transdermal administration of vectors containing polynucleotides encoding wound healing fusion proteins are often preferred routes of administration.

[0203] Adenoviral vectors can be used for short-term or intermediate term expression of the fusion protein in dosages such as those described above. Where longer expression (e.g., about three months, about six months, about nine months or longer) is desired, retroviral vectors (e.g., lentivirus vectors) or adeno-associated viral (AAV) vectors can be advantageously used (as described in, e.g., Buschacher et al., *Blood*, 5(8), 2499-504, Carter, *Contrib. Microbiol.*, 4, 85-86 (2000), Smith-Arica, *Curr. Cardiol. Rep.*, 3(1), 41-49 (2001), Taj, *J. Biomed. Sci.*, 7(4), 279-91 (2000), Vigna et al., *J. Gene Med.*, 2(5), 308-16 (2000), Klimatcheva et al., *Front. Biosci.*, 4, D481-96 (1999), Lever et al., *Biochem. Soc. Trans.*, 27(6), 841-47 (1999), Snyder, *J. Gene Med.*, 1(3), 166-75 (1999), Gerich et al., *Knee Surg. Sports Traumatol. Arthrosc.*, 5(2), 118-23 (1998), and During, *Adv. Drug Deliv. Review*, 27(1), 83-94 (1997), and U.S. Patents 4,797,368, 5,139,941, 5,173,414, 5,614,404, 5,658,785, 5,858,775, and 5,994,136, as well as other references discussed elsewhere herein). Alternatively, polynucleotide vectors can be used, or host integrative techniques

can be employed.

**[0204]** Non-polynucleotide and non-protein factors that are useful for co-administration with the fusion protein, polynucleotide, and vector of the invention, particularly where a polynucleotide encoding a second factor that promotes angiogenesis, bone growth, or wound healing is administered, also can be administered to the cell, tissue or host. Preferred examples of such factors are set forth in U.S. Patent Application 09/832,355.

**[0205]** The fusion protein, polynucleotide, or vector can be administered by or in association with *ex vivo* delivery of cells, tissues, or organs. Therefore, for example, a target tissue can be removed, contacted with the vector composition, and then reimplanted into the host (e.g., using techniques described in or similar to those provided in Crystal et al., *Cancer Chemother. Pharmacol.*, 43(Suppl.), S90-S99 (1999)). *Ex vivo* administration of an angiogenic fusion protein, or preferably angiogenic vector composition, to the target tissue also helps to minimize undesirable induction of angiogenesis in non-targeted tissue. A specific example of such a technique is the administration of an angiogenic vector composition to a tissue flap in surgical procedures involving replacement and/or transfer of tissue flaps (e.g., in breast reconstruction). "Tissue flaps" thus can comprise portions of removed tissue from a living tissue, a tissue of the recently deceased, a tissue from a different species (e.g., a pig tissue, preferably a tissue that is modified to exhibit a reduced immune response upon application to a human), or a synthetically generated tissue. Examples of suitable tissues are described in, e.g., U.S. Patent 6,140,039. Cultures of cells, particularly three-dimensional cultures, which can be a suitable substitute, additive, or alternative to such tissues, also can be administered in association with the fusion protein, polynucleotide, or vector of the invention. Examples of suitable cultures in this respect are provided in U.S. Patents 6,039,760, 6,022,743, 5,902,741, 5,863,531, 5,858,721, 5,849,588, 5,843,766, 5,830,708, 5,785,964, 5,624,840, 5,580,781, 5,578,485, 5,541,107, 5,518,915, 5,516,681, 5,516,680, 5,512,475, and 5,510,254. Related methods and compositions are provided in, e.g., U.S. Patents 6,121,042, 6,060,306, 6,027,306, 6,008,049, 5,928,945, 5,842,477, 5,780,295, 5,714,588, and 5,559,022. Cells that are genetically transformed with the polynucleotides or a host genome integrative vector also can be administered in an *ex vivo* manner to the host (e.g., using the techniques described in, or similar to those described in, U.S. Patent 5,399,346). For example, keratinocytes or fibroblasts can be cultured *in vitro*, transformed so as to produce wound healing fusion protein at high levels, and subsequently administered to a wound site (typically re-administered), thereby effecting long term production of the wound healing fusion protein (via expression), which is particularly preferred in skin regeneration (e.g., in treating severe burns). In other aspects, the fusion protein, polynucleotide, or vector of the invention can be administered with a cell that is modified *ex vivo*, such as activated macrophages (particularly where the treatment of



spinal injuries is sought).

[0206] As previously mentioned, the fusion protein, polynucleotide, vector, together or separately can be co-administered with any suitable factor, preferably a factor which promotes angiogenesis, wound healing, bone growth, related biological activity, or enhances the activity of the fusion protein, polynucleotide or vector. Thus, in some situations, combinations of fusion protein, polynucleotide, or vector and another factor (e.g., bone growth promoting, angiogenic, or wound healing promoting protein), or co-administration of the vector and fusion protein can be desirable. Such co-administration can facilitate a multi-dimensional approach to the treatment of diseases. For example, in the context of angiogenesis-related disorders, such as vascular ischemia, the administration of the fusion protein, fusion protein-encoding polynucleotide, or vector comprising such a polynucleotide can be associated with the administration of a smooth muscle tension modifier (e.g., a vasodilator, such as a direct vasodilator (e.g., hydralazine, minoxidil, reserpine, or combinations thereof), an atrial natriuretic peptide, a vasoactive intestinal peptide, a histamine, an epinephrine or modified epinephrine (e.g., a  $\beta$ -2 receptor targeted epinephrine homolog or a naturally occurring epinephrine administered in a  $\beta$ -2 receptor-targeting manner), a bradykinin, a paracrine which induces vasodilatation (e.g., adenosine, carbon dioxide, hydrogen ion, nitric oxide, or an endothelin), an ACE inhibitor (e.g., an ACE2 inhibitor), an adrenergic receptor blocker, a vascular-associated parasympathetic nervous system stimulator (e.g., acetylcholine), an angiotensin II-receptor blocker (ARB - e.g., tasosartan), and/or a calcium channel blocker). Other suitable non-vasodilator compounds which lower vascular resistance can be administered, and/or the application of mechanical techniques for lowering resistance (and, thus, increasing blood flow) can be applied, near or at tissues associated with the administration of the angiogenic fusion protein, fusion protein-encoding polynucleotide, or vector, and/or at one or more distal/peripheral tissues. Additionally, one or more biologically active catecholamines can be co-administered in association with the fusion protein, polynucleotide, or vector, particularly in association with the administration of an angiogenic fusion protein, polynucleotide, or vector to or near the heart. When an angiogenic fusion protein, polynucleotide, or vector is administered as a prophylactic (e.g., to a tissue at risk of ischemia due to an imminent vascular occlusion), co-administration of a factor which reduces the risk of occlusion, e.g., an anti-coagulant (such as a heparin, antithrombin III, a plasminogen, a prostacyclin (e.g., prostaglandin I or PGI<sub>2</sub>), Protein C, tissue plasminogen activator (t-PA), the anti-coagulants described in U.S. Patent 6,121,435, or homologs thereof), or an LDL cholesterol reducing factor (e.g., a bile acid sequestrant, such as cholestyramine, colestipol, and nicotinic acid (niacin), a statin (HMG CoA reductase inhibitor), such as, lovastatin, pravastatin, simvastatin, and atorvastatin (Lipitor),

rosuvastatin calcium (Crestor), an endothelin agonist (e.g., tezosentan), a gemfibrozil, a probucol, or a clofibrate) also is contemplated. Certain statins (e.g., simvastatin, atorvastatin, mevastatin) have also been reported to stimulate endothelial progenitor cells which may lead to vasculogenesis (Llevadot et al., *J. Clin. Invest.* 108, 399-405 (2001) and Dimmeler et al., *J. Clin. Invest.* 108, 391-397 (2001)). Administration of the fusion protein, polynucleotide, or vector can be in conjunction with a surgical method where an occlusion is removed, or where lipids (e.g., LDL cholesterol) are removed from cells which then are re-administered (i.e., an autotransplant). Administration of the fusion protein, polynucleotide or vector with or in association with a fast-twitch protein (e.g., a prealbumin) can be advantageous, particularly where the treatment of congestive heart failure is desired.

**[0207]** In certain situations, it can be desirable to co-administer a factor that induces or promotes hematopoiesis with the fusion protein, polynucleotide, or vector of the invention. Any suitable hematopoietic factor can be co-administered in any suitable form. The hematopoietic factor can be any suitable type of hematopoietic factor. Examples of such factors include red blood cell growth promoting factors (e.g., erythropoietin (EPO)), megakaryocyte growth promoting factors (e.g., granulocyte-macrophage colony stimulating factor (GM-CSF)), eosinophil growth promoting factors (e.g., GM-CSF), neutrophil growth promoting factors (e.g., granulocyte colony-stimulating factor (G-CSF)), and monocytes growth promoting factors (e.g., macrophage colony-stimulating factor (M-CSF)). Such factors can be administered in association with an administration of stem cells or, more particularly, haematopoietic precursor cells or angioblasts, such as bone marrow derived angioblasts (as described in, e.g., Kocher et al., *Nat. Med.*, 7(4), 430-36 (2001)), or alternatively, an administration of developed cells, such as cardiac myocytes (using techniques described in or similar to those provided in Li et al., *J. Mol. Cell Cardiol.*, 31, 513-22 (1999)). Such cells can be obtained from a heterologous source or from a patient to which they are to be re-administered (e.g., through obtaining such cells from removed (and possibly cultured) bone marrow, blood, or fatty tissues of the individual). Similar co-administration of relevant cells can be performed for wound healing and bone growth promoting aspects of the invention (e.g., co-administration of keratinocytes in wound healing or of osteoblasts for promotion of bone growth). Co-administration of hematopoietic factors is particularly preferred in association with the administration of a wound healing fusion protein, polynucleotide, or vector of the invention.

**[0208]** Factors that block or enhance events in the angiogenic, wound healing, or bone growth promoting pathway also can be administered in association with the fusion protein, polynucleotide, or vector. Co-administration of factors that upregulate expression of a gene or genes encoding a desired angiogenic factor, bone growth promoting factor, or wound

healing promoting factor, where such a factor does not correspond or related to a peptide portion of the fusion protein also is within the scope of the invention (e.g., administration of a factor which upregulates expression of a VEGF). For example, co-administration of PLC- $\gamma$ , Ras, Shc, Nck, PKC and/or PI3-kinase can be co-administered with the polynucleotide, vector, or fusion protein, to induce downstream signal pathways associated with VEGFR-2, as can factors which block such downstream interactions. Factors which induce VEGF gene expression, such as PDGF, keratinocyte growth factor, EGF, TNF- $\alpha$ , IGF-1, thyroid-stimulating hormone, IL-1 $\alpha$ , IL-4, IL-6, TGF- $\beta$ , IL-1 $\beta$ , prostaglandin E2 (PGE<sub>2</sub>), ACTH, v-Ha-ras, v-raf, and v-myc, also can be co-administered with the fusion protein, polynucleotide, or vector, as can chemical agents which upregulate VEGF gene expression, such as phorbol myristate acetate (as described in, e.g., Ilan et al., *J. Cell Sci.*, 111, 3621-31 (1998)) or other phorbol esters. The fusion protein, polynucleotide, or vector can be advantageously administered after or during administration of such a phorbol ester compound, which may induce vascular tube formation in collagenous tissues, as administration of an angiogenic fusion protein may sustain the integrity of the newly formed vascular tube and prevent endothelial cell apoptosis thereafter which might otherwise result from phorbol ester-induced angiogenesis. Progesterone can similarly be co-administered with a fusion protein, polynucleotide, or vector to upregulate HBNF gene expression.

**[0209]** The fusion protein, polynucleotide, or vector also or alternatively can be administered in association with a factor that affects a pathway associated with the biological activity of a wild-type ARF. For example, a Bmx tyrosine kinase (as described in, e.g., Rajantie et al., *Mol. Cell Biol.*, 21(14), 4647-55 (2001)), or polynucleotide encoding a Bmx tyrosine kinase, which is a factor that acts "downstream" of Ang-1 and VEGF in arterial endothelial cell biological pathways, can be co-administered with the fusion protein, polynucleotide, or vector of the invention. Also or alternatively, the fusion protein, polynucleotide, or vector can be administered in association with a factor that induces expression of a wild-type ARF gene. For example, the fusion protein, polynucleotide, or vector of the invention can be co-administered with angiotensin II, Her 2, or leptin (which induce Ang-2 gene expression in adipose tissues), or thrombin (which induces Ang-1 release from platelets), or a polynucleotide encoding such factors or homologs thereof.

**[0210]** In some situations, the fusion protein, polynucleotide, or vector is desirably administered with an integrin, polynucleotide encoding an integrin, or a protein or factor that blocks the activity of an integrin, preferably of an integrin that binds to a wild-type ARF. For example, the fusion protein, polynucleotide, or vector can be administered with an  $\alpha 5$  integrin or a factor that blocks the expression/production of  $\alpha 5$  integrin and/or its binding to Ang-1, Ang-2, and/or the fusion protein of the invention. Also or alternatively, the fusion protein, polynucleotide, or vector can be administered with a vitronectin, a

polynucleotide encoding a vitronectin, or a factor that blocks the expression/production of vitronectin or its binding to Ang-1, Ang-2, and/or the fusion protein of the invention. The fusion protein, polynucleotide, or vector also can be administered with a factor that upregulates the expression of a receptor for the fusion protein. For example, the fusion protein, polynucleotide, or vector can be co-administered with a thyroid stimulating hormone, TNF- $\alpha$ , or a combination of desferrioxamine and cobalt, which upregulate Tie-2 expression.

**[0211]** Factors that inhibit inflammation also or alternatively can be administered with the fusion protein, polynucleotide, or vector of the invention. The inflammation inhibitor can be any suitable inflammation inhibitor. Examples of suitable inflammation inhibitors are provided in, e.g., U.S. Patent 5,830,880. In some circumstances, co-administration of a suitable factor which inhibits thrombosis can be desirable, such as the factors described in U.S. Patent 5,955,576.

**[0212]** Factors which are co-administered with the fusion protein, polynucleotide, or vector of the invention can be co-administered in any suitable manner, and in any suitable order (i.e., concurrently or sequentially), such as administering a fusion protein, polynucleotide, or vector of the invention and separately administering a vector containing a polynucleotide encoding such a factor (or homolog thereof), or administering a vector containing a polynucleotide encoding such a factor which also encodes a fusion protein of the invention.

**[0213]** Factors which reduce naturally occurring anti-angiogenic factors (e.g., an endostatin (or fragment thereof, such as the collagen XVIII fragment), angiotensin (or fragment thereof, such as the plasminogen fragment), thrombospondins (e.g., thrombospondin-1), the 16 kDa fragment of prolactin, and vasostatin (or calreticulin)), Cartilage-derived inhibitor (CDI), CD59 complement fragment, Gro-beta, Heparinases, Heparin hexasaccharide fragment, human chorionic gonadotropin (hCG), IFNs, Interferon inducible protein (IP-10), IL-12, Kringle 5 (plasminogen fragment), 2-Methoxyestradiol, Placental ribonuclease inhibitor, Plasminogen activator inhibitor, Platelet factor-4 (PF4), Proliferin-related protein (PRP), Retinoids, Tetrahydrocortisol-S, other anti-angiogenic C-X-C chemokines, Yes and Src (as described in International Patent Application WO 01/45751), and/or vasculostatin also can be suitable for co-administration with the fusion protein, polynucleotide, or vector. For example, one or more factors which block one or more anti-angiogenic factors from binding with receptors required for activation, or which prevent cleavage or other conformational changes required for immature anti-angiogenic proteins to develop anti-angiogenic activity (e.g., blocking cleavage required for development of a mature, anti-angiogenic, endostatin, or preventing conversion of plasminogen to angiotensin), can be administered with the angiogenic fusion protein,

polynucleotide, or vector. Such factors can be administered in any suitable form (e.g., as a polynucleotide inserted into a separate vector or the same vector with a fusion protein-encoding polynucleotide). Alternatively, one or more antisense polynucleotides that prevent transcription and/or translation of an anti-angiogenic gene, or one or more monoclonal antibodies that deactivate the anti-angiogenic factor or block its activity. In some situations, the inventive method comprises blocking the expression or activity of native Ang-2, such that the angiogenic activity of the fusion protein is not impeded by it, particularly where the fusion protein contains an Ang-1 peptide portion.

**[0214]** Administration of anti-angiogenic factors or angiogenic factor antagonists in association with the administration of angiogenic fusion proteins, polynucleotides, and/or vectors can be desirable in some conditions. For example, administration of such factors can provide control over the level of blood vessel growth and/or vascular permeability to be achieved by administration of the fusion protein, polynucleotide, or vector. In a preferred aspect, the fusion protein, fusion protein-encoding polynucleotide, or fusion protein-producing vector is administered with a PEDF anti-angiogenic protein, PEDF polynucleotide (or PEDF homolog polynucleotide), or vector comprising such a PEDF polynucleotide (such proteins, polynucleotides, and vectors are described in, e.g., U.S. Patent 5,840,686 and International Patent Applications WO 95/33480 and WO 01/58494). Alternatively or additionally, the second nucleic acid sequence can comprise a PEDF gene or homolog thereof. Such methods are particularly preferred wherein the fusion protein promotes blood vessel maturation. A particularly preferred combination of PEDF protein, PEDF polynucleotide (whether separate from the fusion protein or fusion protein-producing constructs of the invention or as the second nucleic acid sequence encoded by the fusion protein-encoding polynucleotide), or PEDF vector and a fusion protein, fusion protein polynucleotide, or fusion protein-encoding vector, comprises co-administration to the eye to treat or prevent macular degeneration.

**[0215]** The fusion protein of the invention can be used in any manner that is suitable for one of its constituent peptide portions (examples of such uses are described herein and/or in the references cited herein). Thus, a fusion protein comprising, for example, portions with significant homology to Ang-2, NL4, or CDT6 can be suitable for inhibition of angiogenesis. This includes the use of the fusion protein for treatment of ocular diseases dependent on angiogenesis, such as corneal graft neovascularization, retrolental fibroplasias, diabetic retinopathy, and neovascular diseases of the eye (as described in, e.g., International Patent Application WO 01/29085). Additionally, the fusion protein can be used to treat other diseases which are associated with angiogenesis, including angiofibroma, Osler-Weber syndrome, psoriasis, solid tumors, trachoma, hemophilic joints, vascular adhesions, and hypertrophic scars (as described in, e.g., International Patent Application

WO 01/29085). The fusion protein can also be used to treat immune related and inflammatory diseases (as described in, e.g., International Patent Application WO 00/73452). In contexts where the fusion protein, polynucleotide, or vector is used to treat cancer, for example by reducing angiogenesis, the fusion protein, polynucleotide, or vector can be co-administered with tumor reducing agents (e.g., chemotherapy, radiation therapy, or reoviruses).

**[0216]** In addition to the other administration techniques described herein, the vector composition or fusion protein composition can be administered by direct surgical implantation. Alternatively or additionally, the fusion protein and/or vector composition can be co-administered with a group of therapeutic cells, e.g., stem cells, macrophages, or neutrophils. For example, an angiogenic vector composition of the invention can be co-administered with stem cells to an ischemic location in the heart. The use of the vector composition and fusion protein of the invention also can be useful in organ generation and organ transfer. Stem cell administration can be associated with administration of stem cell-determining factors, such as a Casanova gene homolog (as described in, e.g., Stainier, *Genes Devel.*, 15, 1493-1505 (2001)) or other suitable determining factor. Cord blood also can be advantageously co-administered with the fusion protein, polynucleotide, or vector. The administration of the fusion protein, polynucleotide, or receptor also can be advantageously associated with percutaneous *in situ* coronary venous arterialization (PICVA) (as described in e.g., Vesterle et al., *Circulation*, 103(21), 2539-43 (2001)).

**[0217]** The angiogenic fusion protein and vector compositions of the invention can be used to treat a wide variety of ailments including, e.g., coronary artery disease, peripheral vascular disease, congestive heart failure (e.g., left ventricular dysfunction and left ventricular hypertrophy), neuropathy (peripheral or otherwise), avascular necrosis (e.g., bone or dental necrosis), mesenteric ischemia, impotence (or erectile dysfunction), incontinence, arterio-venous fistula, veno-venous fistula, stroke, cerebrovascular ischemia, muscle wasting, pulmonary hypertension, gastrointestinal ulcers, vasculitis, non-healing ischemic ulcers, retinopathies, restenosis, cancer, orthosclerosis, radiation-induced tissue injury (such as that common with cancer treatment), and other hypoxia-associated or low blood perfusion-associated disorders. In addition, the angiogenic fusion protein and vector compositions also find utility in the study and/or aid of wound healing (e.g., healing of ischemic ulcers), plastic surgery procedures (e.g., healing or reattachment of skin and/or muscle flaps), prosthetic implant healing, vascular graft patency, and transplant longevity. Thus, the invention provides methods of treating such ailments by administration of the fusion protein and/or vector compositions.

**[0218]** The fusion protein, fusion protein-encoding polynucleotide, and vector of the invention are believed to be useful in several medically related contexts. For example, in

surgical contexts, the fusion protein, polynucleotide, and/or vector can be used to treat orthopedic surgery-associated avascular necrosis, treat mesenteric ischemia, provide prophylaxis against ischemia in association with ostomies, treat or provide prophylaxis for thoracic ischemia related spinal chord complications (aneurysm repairs), treat sexual dysfunction (e.g., urology-postprostatectomy associated sexual dysfunction – for example in association with radical prostatectomy), provide smooth muscle tone in tissues (e.g., treat incontinence), prevent radiation-induced vascular necrosis (e.g., prevent tooth loss associated with radiation use in dentistry), promote gum and/or tooth regeneration, create and/or promote veno-venous or arterio-venous anastomosis, and enhance cartilage, tendon, and/or ligament repair replacement (either through direct healing or by promoting angiogenesis in such tissues or tissues associated therewith).

**[0219]** The fusion protein, polynucleotide, and vector of the invention also can be useful in neurological applications, such as inducing angiogenesis in the treatment of cerebrovascular-associated vascular obstructive disease. Pulmonary and gastrointestinal applications of the fusion protein, polynucleotide, and vector include administration in association with liver regeneration, treatment of pulmonary hypertension, and providing/increasing blood supply to a transplanted lung. Rheumatological/renal applications of the fusion protein, polynucleotide, and vector include the treatment of vasculitis, modulation of renal permeability and function, modulation of peritoneal permeability and function, and promotion or prevention of growth factor delivery to such tissues through such permeability modulation.

**[0220]** The fusion protein, polynucleotide, or vector also can be used to reduce or prevent tumor growth. Fusion proteins comprising an Ang-2, Ang-2X, or Ang-2 homolog peptide portion (and corresponding polynucleotides and vectors) are preferred in this respect.

**[0221]** A preferred aspect of the invention comprises the administration of a vector comprising a nucleic acid encoding a fusion protein of the invention under one promoter and a second nucleic acid sequence encoding a second protein, desirably an angiogenic factor (e.g., a VEGF), under the control of a second promoter, where the first promoter and second promoter have different expression profiles and/or are differentially inducible. Desirably, after administration of the vector to a suitable cell, tissue, or mammal, the first nucleic acid sequence is permitted, induced, or upregulated to express the nucleic acid sequence encoding the fusion protein, and the second nucleic acid is permitted, induced, or upregulated to express the second factor, in a manner which mimics a biological cascade as described elsewhere herein. The method can be applied with more than two factors (e.g., 3, 4, or more factors) to mimic more complex cascades. Constructs for practicing such methods are described elsewhere herein.

[0222] The methods of this invention are closely related in function. Thus, it is to be understood that the disclosure with respect to any aspect of the invention can be applied to any other suitable aspect. For example, forms of administration and delivery techniques for fusion protein compositions can be used for polynucleotide or, more particularly, vector compositions, and vice versa. Similarly, a reference to administration of the fusion protein, polynucleotide, or vector of the invention encompasses the administration of a pharmaceutically acceptable composition containing the fusion protein, polynucleotide, or vector, as applicable.

[0223] The invention further provides Ang-2X, and polynucleotides encoding Ang-2X, as described in, e.g., Example 1, and modified by the techniques and principles applicable to the fusion proteins and fusion protein-encoding polynucleotides of the invention. The Ang-2X peptide provided by the invention can be administered and produced according to the methods described herein with respect to the fusion proteins of the invention. Ang-2X can be inserted into a vector using the techniques described herein with respect to fusion protein-encoding polynucleotides of the invention. As such, the invention provides vectors comprising Ang-2X-encoding polynucleotides, methods of producing Ang-2X peptides, and methods of using such Ang-2X peptides, polynucleotides, or vectors to treat disease, and, most preferably, to modulate angiogenesis.

[0224] The methods of using the fusion proteins of the invention, Ang-2X, and related polynucleotides and vectors described herein, can be applied to any suitable ARFs, such as Ang-1, Ang-2, Ang-3, Ang-4, NL1, NL2, NL3, NL4, NL5, FLS139, NL7, NL8, and murine FDRG. Thus, the invention provides novel methods of using such factors, and polynucleotides encoding them. For example, the invention provides a replication-deficient adenoviral vector comprising a gene encoding NL1, NL5, or a codon optimized angiopoietin, and a second gene encoding another angiogenic factor (e.g., a HBNF, MK, or VEGF (preferably a non-heparin-binding VEGF, such as VEGF<sub>121</sub>)). Additionally, for example, the invention provides a method of promoting angiogenesis comprising infecting a cell with such a viral vector, preferably at the dosages described elsewhere herein. The invention also provides the application of the techniques described herein to obtain novel homologs of such wild-type ARFs and the novel homologs thereby obtained. For example, the invention provides codon optimized Ang-1 genes (SEQ ID NO: 167), and vectors comprising polynucleotides encoding such genes.

[0225] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[0226]

[0227] EXAMPLE 1

[0228] This example describes the generation of the novel Angiopoietin-2 homolog



Ang-2X.

[0229] Ang-2X was derived from the results of a TNBLAST search of the high-throughput sequence database for the human genome project for sequences exhibiting significant levels of identity to Ang-1. Hits were identified on BAC clone RP11-16g12 (GenBank accession number AC018398). Nine contigs were identified and assembled by joining (complement 335846...336136), (complement 265610...265440), (complement 133812...133693), (complement 302082...302315), (complement 52191...52060), (complement 238562...238455), (complement 47913...47746), (complement 141153...141079), and (complement 18606...18544) to derive the following polynucleotide sequence:

[0230]

[0231] ATGTGGCAGATTGTTTTCTTTACTCTGAGCTGTGATCTTGTCTTGGCCG  
CAGCCTATAACAACCTTTCGGAAGAGCATGGACAGCATAGGAAAGAAGCAATATC  
AGGTCCAGCATGGGTCCTGCAGCTACACTTTCCTCCTGCCAGAGATGGACAACTG  
CCGCTCTTCTCCAGCCCCCTACGTGTCCAATGCTGTGCAGAGGGACGCGCCGCTC  
GAATACGATGACTCGGTGCAGAGGCTGCAAGTGCTGGAGAACATCATGGAAAAC  
AACACTCAGTGGCTAATGAAGGTAGAGAATATATCCCAGGACAACATGAAGAAA  
GAAATGGTAGAGATACAGCAGAATGCAGTACAGAACCAGACGGCTGTGATGATA  
GAAATAGGGACAAACCTGTTGAACCAAACAGCGGAGCAAACGCGGAAGTTAACT  
GATGTGGAAGCCCAAGTATTAAATCAGACCACGAGACTTGAACCTCAGCTCTTGG  
AACACTCCCTCTCGACAAACAAATTGGAAAAACAGATTTTGGACCAGACCAGTG  
AAATAAACAAATTGCAAGATAAGAACAGTTTCCTAGAAAAGAAGGTGCTAGCTA  
TGGAAGACAAGCACATCATCCAACCTACAGTCAATAAAAGAAGAGAAAGATCAGC  
TACAGGTGTTAGTATCCAAGCAGAATTCCATCATTGAAGAACTCGAAAAAAAAA  
TAGTGACTGCCACGGTGAATAATTCAGTTCTTCAGAAGCAGCAACATGATCTCAT  
GGAGACAGTTAATAACTTACTGACTATGATGTCCACATCAAACGCAGCTAAGGA  
CCCCACTGTTGCTAAAGAAGAACAATCAGCTTCAGAGACTGTGCTGAAGTATTC  
AAATCAGGACACACCACGAATGGCATCTACACGTTAACATTCCCTAATTCTACAG  
AAGAGATCAAGGCCTACTGTGACATGGAAGCTGGAGGAGGCGGGTGGACAATTA  
TTCAGCGACGTGAGGATGGCAGCGTTGCATTTAGAGGACTTGGAAAGAATATA  
AAGTGGGATTTGGTAACCTCTCAGAAAAATATTGGCTGGGAAATGAGTTTGTTC  
GCAACTGACTAATCAGCAACGCTATGTGCTTAAAATACACCTTAAAGACTGGGA  
AGGGAATGAGGCTTACTCATTGTATGAACATTTCTATCTCTCAAGTGAAGAACTC  
AATTATAGGNNNNNNNNNNNNNNNNNNNNNGGCAATGATTTTAGCACAAGGGATG  
GAGCCACCGNCANATGTATTTGCAAATGTTCACAAATGCTAACAGNAGGTNNNN  
NNNNNNNNNNNNNNNNNNNNNNNNNNNTACTGGAAAGGCTCAGGCTATTCGCTC  
AAGGCCACAACCATGATGATCCGACCAGCAGATTTC [SEQ ID NO: 160]

[0232]

[0233] where N represents any polynucleotide. A polynucleotide having this sequence is generated using any standard polynucleotide synthesis.

[0234] The Ang-2X polynucleotide is predicted to encode a polypeptide having the following amino acid sequence:

[0235]

[0236] Met Trp Gln Ile Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys Leu Glu Asn Ile Ser Gln Asp Asn Met Lys Lys Glu Met Val Glu Ile Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Ile Glu Ile Gly Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu Leu Gln Leu Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp Gln Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu Lys Lys Val Leu Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser Ile Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn Ser Ile Ile Glu Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn Asn Leu Leu Thr Met Met Ser Thr Ser Asn Cys Lys Xaa Xaa Xaa Xaa Val Ala Lys Glu Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe Lys Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Met Trp Gln Ile Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr [SEQ ID NO: 174]

[0237]

[0238] where Xaa represents any amino acid residue. Ang-2X is believed to have angiogenesis modulating activities similar to angiopoietins, and particularly to Ang-2.

[0239]

[0240] EXAMPLE 2

[0241] This example demonstrates the production of a polynucleotide encoding a fusion protein of the invention, the insertion of the polynucleotide into a suitable vector, and the expression of the fusion protein-encoding polynucleotide resulting in production of the fusion protein.

[0242] A first polynucleotide comprising a sequence encoding Ang-2X CCD1 is generated by standard polynucleotide synthesis techniques. A second polynucleotide comprising a sequence encoding the Ang-1 FLD is produced by standard polynucleotide synthesis techniques. The first polynucleotide and second polynucleotide are fused, using

standard techniques, to form a fused polynucleotide.

[0243] The oligonucleotide primers AGTAATGCAGTCCAAAGAGACG (SEQ ID NO: 168) and AAAGTCTAGTGGTTCGATCATCA (SEQ ID NO: 169) are used to amplify a PCR product encoding a fusion protein comprising a modified Ang-2X CCD1 variant, which lacks the N-terminal valine residue of Ang-2X CCD1 (SEQ ID NO: 170), directly fused to the Ang-1 FLD from the fused polynucleotide. The PCR product, first polynucleotide, or third polynucleotide optionally can be fused to an additional sequence encoding a wild-type ARF signal sequence and/or variable domain (such that the variable domain and/or signal sequence is positioned N-terminal to the Ang-2X CCD1 variant sequence).

[0244] The Ang-2X CCD1 variant/Ang-1 FLD fusion protein-encoding PCR product is cut with *Xho* I to obtain a sequence encoding a fusion protein comprising an Ang-2X CCD1-derived CCD, which lacks the ten N-terminal residues of Ang-2X CCD1 (hereinafter referred to as Ang-2X CCD4) (SEQ ID NO: 171) fused to the Ang-1 FLD. The fusion protein-encoding polynucleotide (SEQ ID NO: 172) is cloned into a pAd3511CMV transfer vector, which comprises nucleotides 1-4511 of the adenoviral serotype 5 genome, except nucleotides 353-3511 (which encompass the adenoviral E1A and E1B coding regions), the CMV promoter, a multiple cloning site (including *Xho* I), an SV40 poly A site, and a splice donor/acceptor site between Ad5 nucleotides 353 and 3511.

[0245] After insertion of the *Xho* I fragment, the recombinant transfer vector is used to generate a transfection plasmid capable of producing an E1-deleted adenoviral vector containing the Ang-2X CCD4/Ang-1 FLD fusion protein-encoding sequence positioned in the E1 deletion upon transfection into a suitable host cell. The transfection plasmid is generated by any suitable technique. Examples of such techniques include homologous recombination, or ligation to, one or more additional plasmids comprising the remainder of the adenoviral genome except the desired deleted regions (i.e., E1, E3, and optionally other regions, e.g., the E4 region). Any suitable homologous recombination technique can be used to generate the vector-producing plasmid. Examples of such techniques are provided in, e.g., Chinnadurai et al., *J. Virol.*, 32, 623-28 (1979), Berkner et al., *Biotechniques*, 6, 616-28 (1998), Chartier et al., *J. Virol.*, 70, 4805-10 (1996), and International Patent Application WO 96/25506. A preferred homologous recombination technique is described in International Patent Application WO 99/15686. Alternatively, any suitable ligation technique can be used, such as the techniques described in, e.g., Stow, *J. Virol.*, 37(1), 171-80 (1981), Stow, *Nucl. Acids Res.*, 10(17), 5105-19 (1982), and Berkner et al., *Nucl. Acids Res.*, 11(17), 6003-20 (1983).

[0246] After a suitable transfection plasmid containing the Ang-2X CCD4/Ang-1 FLD fusion protein-encoding sequence is generated, the transfection plasmid is transfected into a

suitable E1 complementing cell line, such as a 293-ORF6 cell line (described in International Patent Application WO 95/34671), using standard techniques (e.g., calcium phosphate precipitated transfection), thereby resulting in the production of a stock of E1-deleted, replication-deficient, adenoviral vectors. Preferably, the vector-cell line system selected is such that replication competent adenovirus (RCA) levels in the stock are confirmed to be less than about  $1 \times 10^7$  plaque forming units (pfu), preferably by using the techniques described in U.S. Patent 5,994,106. Levels of viral pfu can be determined using standard techniques (such as the techniques described in Chinnadurai et al., *supra* and Precious et al., "Purification and Titration of Adenoviruses" in *VIROLOGY: A PRACTICAL APPROACH*, 193-205 (Mahay et al., Eds., IRL Press 1985)).

[0247] The Ang-2X CCD4/Ang-1 FLD vector is administered by needle injection in an appropriate carrier to at least one target location in a mammalian host. Resultant Ang-2X CCD4/Ang-1 FLD fusion gene expression is confirmed by mRNA expression analysis, subsequent administration of an anti-Ang-1 and/or anti-Ang-2X antibodies to the site of vector administration after sufficient time for fusion protein expression, and/or observation of the angiogenic effects of administering the vector, for example, by using the mouse ear or rat hind limb models for testing the angiogenesis-inducing capacity of a molecule, as described in more detail here.

[0248] In the mouse ear model,  $10^9$ - $10^{10}$  particles units (pu) of the Ang-2X CCD4/Ang-1 FLD vector and a similar dosage of AdVEGF<sub>121</sub>, which contains the human VEGF<sub>121</sub> gene, are administered to Apo E<sup>-/-</sup> mice. All injections are delivered subcutaneously at the base of the ears of anesthetized mice (12 mg/kg xylazine and 60 mg/kg ketamine, IP). Gross morphological changes to the target tissue are observed at various days post-injection. Serial laser Doppler perfusion measurements are taken at various time points post-injection. Changes in blood vessel number are identified using an Olympus BX40F microscope at 400X to examine harvested ears that are perfusion fixed and embedded in paraffin. Control groups receiving similarly administered AdVEGF<sub>121</sub> and/or null vectors are used for comparative testing.

[0249] It is expected that at about four days post-injection, administration of the Ang-2X CCD4/Ang-1 FLD adenoviral vector with AdVEGF<sub>121</sub> and resulting production of the Ang-2X CCD4/Ang-1 FLD fusion protein and VEGF<sub>121</sub> will result in the formation of blood vessels in greater number and/or volume of blood vessels which exhibit a greater level of vessel maturation than vessels resulting from administration of only AdVEGF<sub>121</sub>.

[0250] It is expected that at about 14-28 days post-injection, animals receiving the Ang-2X CCD4/Ang-1 FLD adenoviral vector and AdVEGF<sub>121</sub> in the hind limb model will exhibit tissue perfusion levels higher and/or less blood vessel leakage than in control groups receiving administration of only AdVEGF<sub>121</sub> and or a null vector.

**[0251]** This Example provides a suitable vector comprising a polynucleotide encoding an ARF fusion protein, which, when produced by expression, promotes angiogenesis. The steps recited in the present Example (e.g., selection of appropriate primers for a wild-type ARF FLD and CCD, amplification thereof to form a fusion protein-encoding polynucleotide, insertion of the fusion protein-encoding polynucleotide into a suitable vector, and expression of the polynucleotide therein to produce the fusion protein) can be applied to any suitable combination of ARF-encoding polynucleotide sequences as a viable strategy for obtaining novel ARF fusion proteins by routine experimental techniques.

**[0252]**

**[0253]** All amino acid or nucleotide sequences of one of the aforementioned sequence patterns are to be considered individually disclosed herein. Thus, for example, an amino acid sequence pattern of three residues, where a "Xaa" represents one of the amino acid positions in the pattern represents a disclosure of at least twenty different sequences (i.e., one sequence for each naturally occurring amino acid residue that could be present in the Xaa position).

**[0254]** All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

**[0255]** The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Terms such as "including," "having," "comprising," "containing," and the like are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise indicated, and as encompassing the phrases "consisting of" and "consisting essentially of." Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value of the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

**[0256]** Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred

embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

## WHAT IS CLAIMED IS:

1. A fusion protein comprising:
  - (a) a fibrinogen-like domain that exhibits at least about 75% amino acid sequence identity to the fibrinogen-like domain of a first wild-type protein, which binds a receptor that, when activated, promotes or inhibits angiogenesis, and
  - (b) a coiled-coil domain that exhibits at least about 75% amino acid sequence identity to the coiled-coil domain of a second wild-type protein, which increases the affinity of the fusion protein for the receptor, promotes formation of a multimer comprising the fusion protein, or both,

wherein the first protein and second protein are different, the first protein and second protein exhibit at least about 30% overall amino acid sequence identity with Ang-1, and the first protein, the second protein, or both proteins, are not Ang-1, Ang-2, Ang-3, or Ang-4.
2. The fusion protein of claim 1, wherein the fibrinogen-like domain comprises a first sequence of the sequence pattern Glu Phe/Tyr/His Trp Leu Gly Leu/Asn Glu/Asp Xaa Val/Ile/Leu Xaa Xaa Ile/Leu Xaa<sub>(12-14)</sub> Asp Trp and a second sequence of the sequence pattern Phe Ser Thr Xaa Asp Xaa Asp Asn/His Xaa<sub>3-10</sub> Cys Ala/Ser Xaa<sub>4</sub> Gly Gly Trp Trp Xaa<sub>(2-4)</sub> Cys, wherein the first sequence is positioned N-terminal to the second sequence.
3. The fusion protein of claim 2, wherein the first sequence is of the sequence pattern Phe Ser Thr Lys/Leu Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Ala/Ser Gln/Leu Met/Val Leu/Met Tyr/Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly Pro/Leu Ser Asn Leu Gly and the second sequence is of the sequence pattern Glu Tyr/His Trp Leu Gly Asn Glu Xaa Val/Ile Xaa<sub>(2)</sub> Ile/Leu Thr Xaa Gln/Arg Xaa Xaa Tyr Xaa Leu Arg/Lys Ile/Val Glu Leu Xaa Asp Trp Glu Gly.
4. The fusion protein of claim 1, wherein the second protein is NL1, FLS 139, NL3, NL4, NL5, NL8, zapo1, or murine FDRG.
5. The fusion protein of claim 4, wherein the first protein is the KIA003-associated protein (KAP) or an angiopoietin.
6. The fusion protein of claim 1, wherein the first protein is NL1, FLS 139, NL3, NL4, NL5, NL8, zapo1, or murine FDRG.
7. The fusion protein of claim 6, wherein the second protein is an angiopoietin.

8. The fusion protein of claim 1, wherein the first protein or the second protein is Ang-2X.

9. The fusion protein of claim 1, wherein

(a) the fibrinogen-like domain and coiled-coil domain are directly fused and the amino acid sequence within about 20 amino acid residues of the junction of the fibrinogen-like domain and coiled-coil domain does not form a complex with an MHC Class I molecule, an MHC Class II molecule, or both, when the fusion protein is produced in, or administered to, a mammalian host, or

(b) the fusion protein comprises a linker positioned between the fibrinogen-like domain and the coiled-coil domain, such that the amino acid sequence within about 20 amino acid residues of the linker does not form a complex with an MHC Class I molecule, an MHC Class II molecule, or both, when the fusion protein is produced in, or administered to, a mammalian host.

10. The fusion protein of any of claims 1-9, wherein the fusion protein reduces blood vessel leakage when administered or produced *in vivo*, promotes blood vessel maturation when administered or produced *in vivo*, or both.

11. The fusion protein of any of claims 1-9, wherein the fusion protein, when administered or produced in a mammalian host, exhibits a half-life which is at least 125% as long as the half-life of Ang-1.

12. A fusion protein comprising:

(a) a fibrinogen-like domain that exhibits at least about 30% amino acid sequence identity to the fibrinogen-like domain of Ang-1, and

(b) a coiled-coil domain that comprises

(1) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the coiled-coil domain of zapo1, murine FDRG, or both,

(2) an amino acid sequence that exhibits at least about 50% amino acid sequence identity to the coiled-coil domain of NL1, NL5, or both,

(3) an amino acid sequence that exhibits at least about 40% amino acid sequence identity to the coiled-coiled domain of NL8,

(4) an amino acid sequence that exhibits at least about 25% amino acid sequence identity to the coiled-coiled domain of FLS 139, or

(5) an amino acid sequence that fulfills any combination of (1)-(4),



wherein *in vivo* administration or production of the fusion protein promotes or inhibits angiogenesis in a mammalian host.

13. The fusion protein of claim 12, wherein
  - (a) the fibrinogen-like domain exhibits at least about 50% amino acid sequence identity to the fibrinogen-like domain of Ang-1,
  - (b) the coiled-coil domain exhibits less than about 30% amino acid sequence identity to the coiled-coil domains of Ang-1, Ang-2, Ang-3, and Ang-4, or
  - (c) both (a) and (b).
14. A fusion protein comprising:
  - (a) a fibrinogen-like domain that comprises
    - (1) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the fibrinogen-like domain of NL1, NL5, NL8, or any combination thereof,
    - (2) an amino acid sequence that exhibits at least about 60% amino acid sequence identity to the fibrinogen-like domain of NL4,
    - (3) an amino acid sequence that exhibits at least about 40% amino acid sequence identity to the fibrinogen-like domain of zapo1, murine FDRG, or both,
    - (4) an amino acid sequence that exhibits at least about 45% amino acid sequence identity to the fibrinogen-like domain of NL3,
    - (5) an amino acid sequence that exhibits at least about 30% amino acid sequence identity to the fibrinogen-like domain of FLS 139, or
    - (6) an amino acid sequence which fulfills any combination of (1)-(5), and
  - (b) a coiled-coil domain that exhibits at least about 35% amino acid sequence identity to the coiled-coil domain of Ang-1, Ang-2, Ang-2X, Ang-3, Ang-4, or any combination thereof.
15. The fusion protein of claim 14, wherein
  - (a) the coiled-coil domain exhibits at least about 65% amino acid sequence identity to the coiled-coil domain of at least one of Ang-1, Ang-2, or Ang-2X, or
  - (b) the coiled-coil domain exhibits at least about 50% amino acid sequence identity to the coiled-coil domain of Ang-3, Ang-4, or both.

16. The fusion protein of claim 15 or claim 16, wherein the fibrinogen-like domain exhibits less than about 45% amino acid sequence identity to the fibrinogen-like domains of Ang-1, Ang-2, Ang-3, and Ang-4.
17. A polynucleotide comprising a nucleic acid sequence encoding the fusion protein of any of claims 1-16.
18. A replication-deficient and non-integrating vector comprising the polynucleotide of claim 17.
19. The vector of claim 18, wherein the polynucleotide comprises a first nucleic acid sequence encoding the fusion protein and a second nucleic acid sequence encoding an angiogenic factor.
20. The vector of claim 19, wherein the first nucleic acid sequence is operably linked to a first expression control sequence, and the second nucleic acid sequence is operably linked to a second expression control sequence, such that the expression of the first and second nucleic acid sequences is initiated at different times, upregulated at different times, initiated in response to different factors, upregulated in response to different factors, or any combination thereof.
21. The vector of claim 19 or claim 20, wherein the second nucleic acid sequence encodes a non-heparin-binding VEGF.
22. A method of promoting angiogenesis in an individual comprising administering to the individual an amount of the fusion protein of any of claims 1-16 effective to promote angiogenesis.
23. The method of claim 22, wherein the method comprises co-administering at least one additional angiogenic factor.
24. The method of claim 22 or claim 23, wherein the method comprises co-administering a non-heparin-binding VEGF, a polynucleotide comprising a nucleic acid sequence encoding a non-heparin-binding VEGF, or a vector comprising a polynucleotide encoding a non-heparin-binding VEGF.

25. A method of producing a fusion protein comprising introducing the polynucleotide of claim 17 into a cell such that the nucleic acid sequence is expressed to produce a fusion protein.

26. The method of claim 25, wherein the cell is in a mammal.

27. The method of claim 25 or claim 26, wherein the polynucleotide is introduced into the cell via the vector of any of claims 18-21.

28. A method of promoting angiogenesis in an individual comprising introducing the vector of claim 20 into a cell and permitting, inducing, or upregulating expression of the first nucleic acid sequence, the second nucleic acid sequence, or both.

FIG. 1

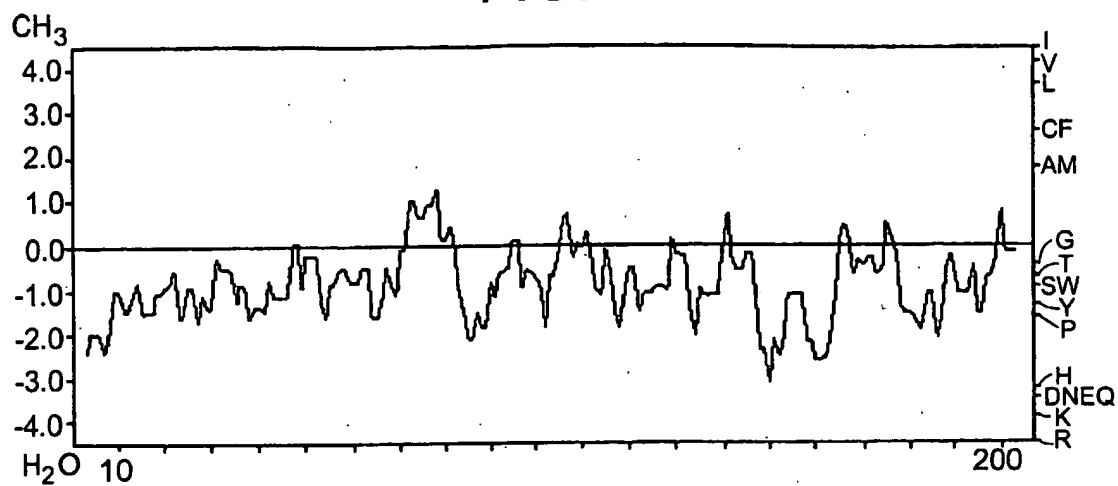
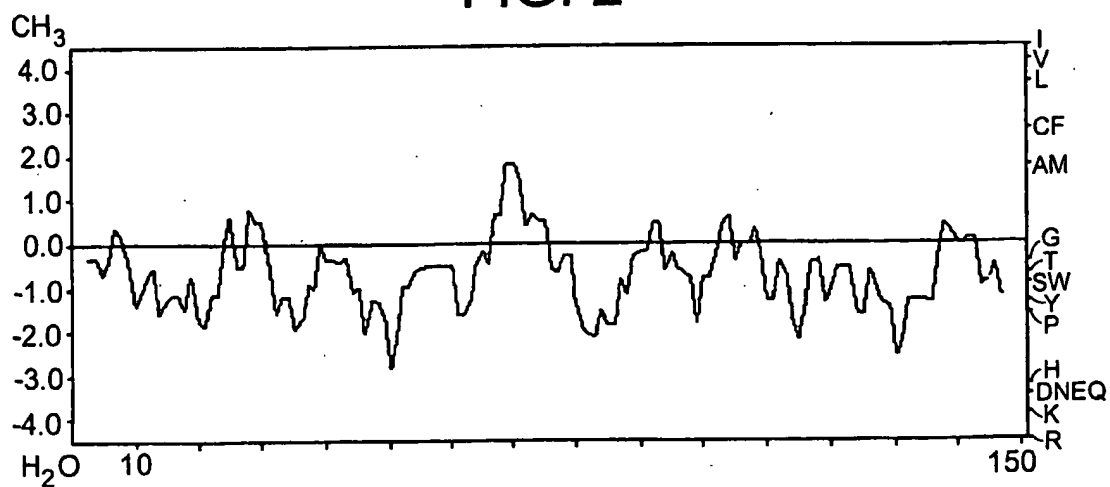


FIG. 2



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FIG. 3

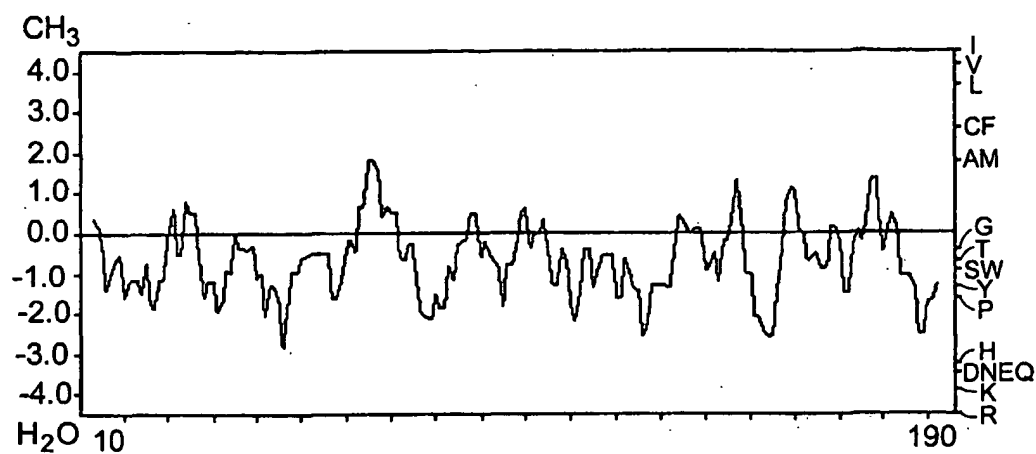
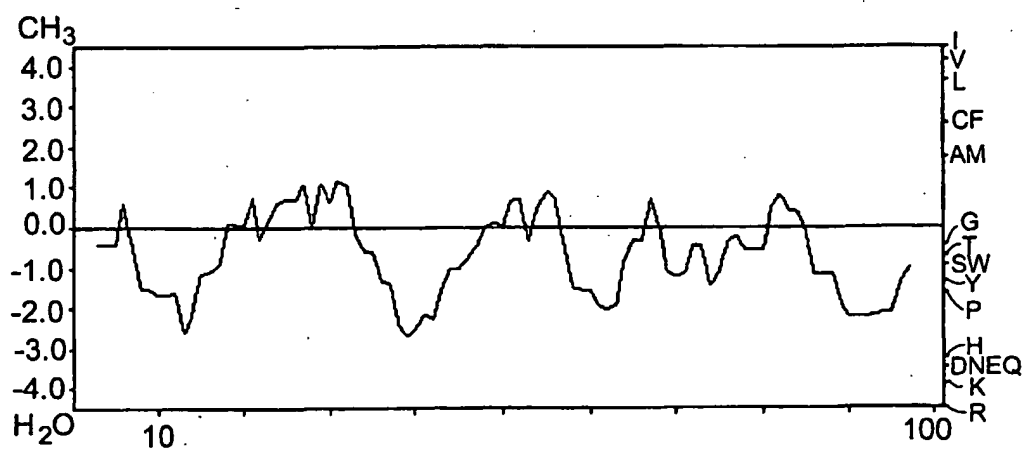
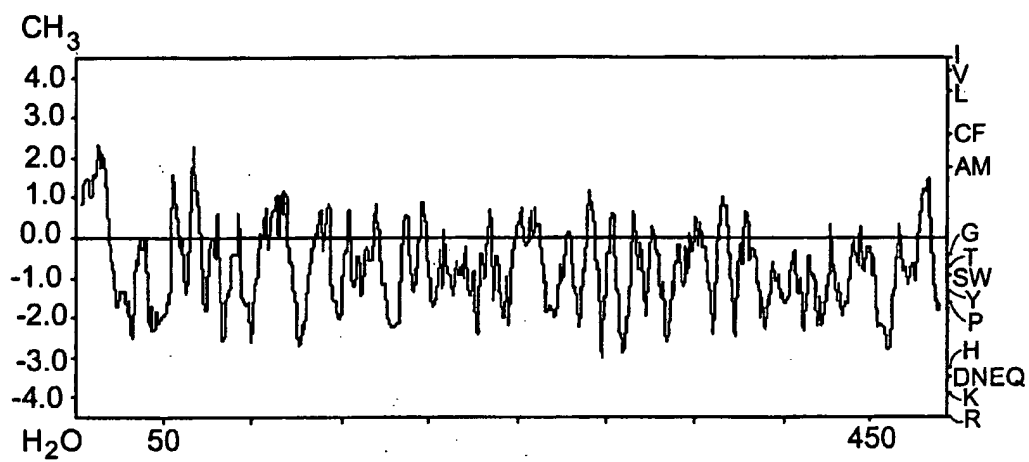


FIG. 4



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FIG. 5



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FIG. 6

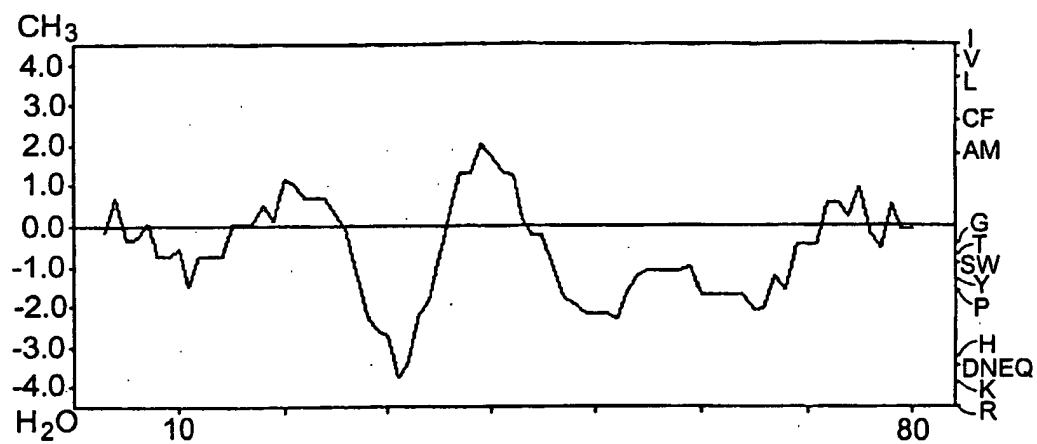
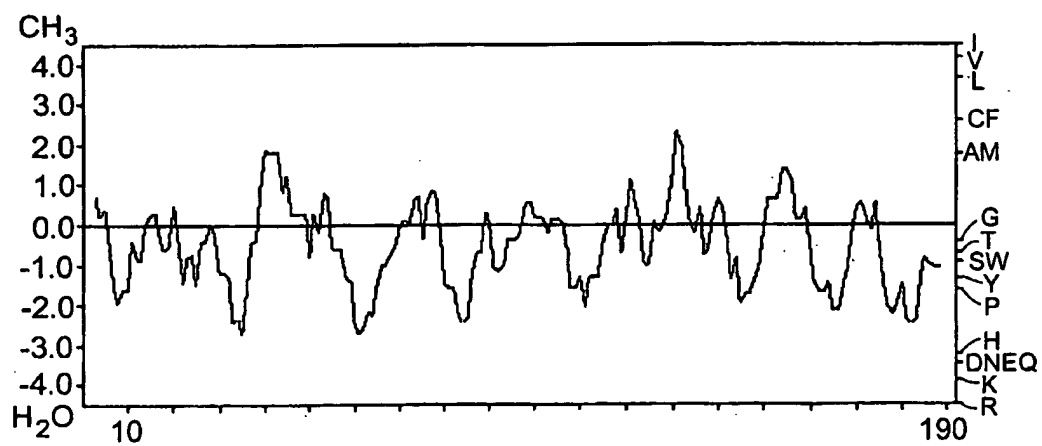


FIG. 7



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FIG. 8

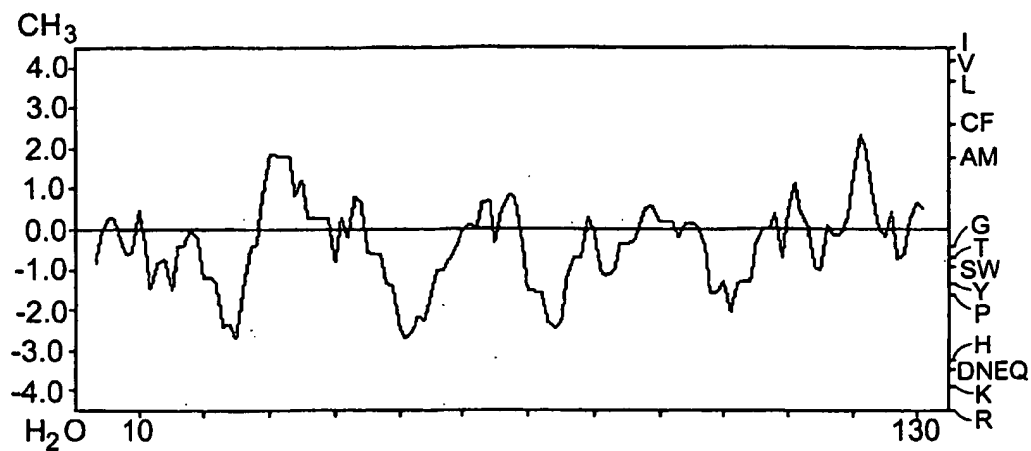
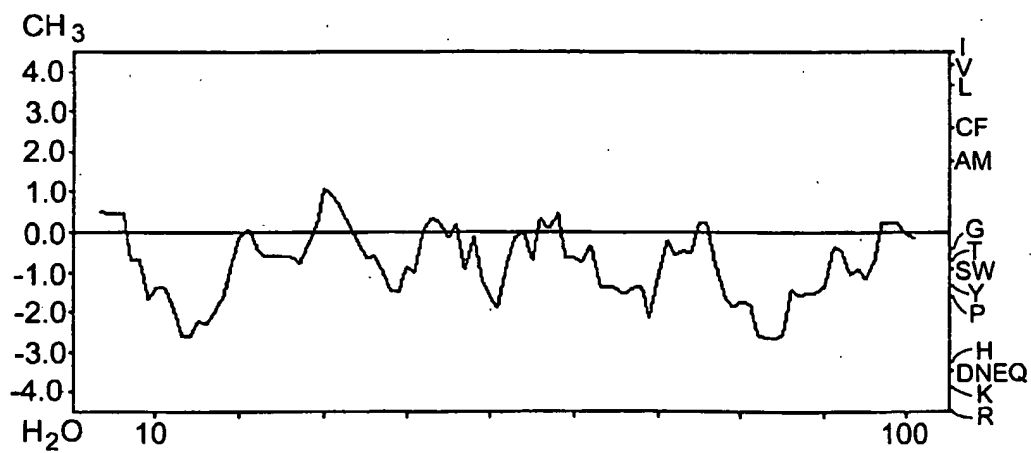


FIG. 9





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FIG. 10

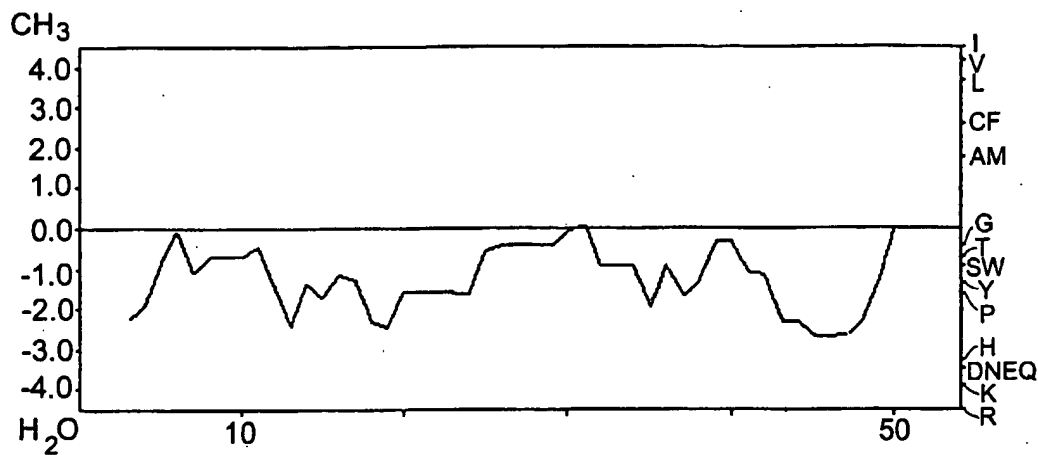
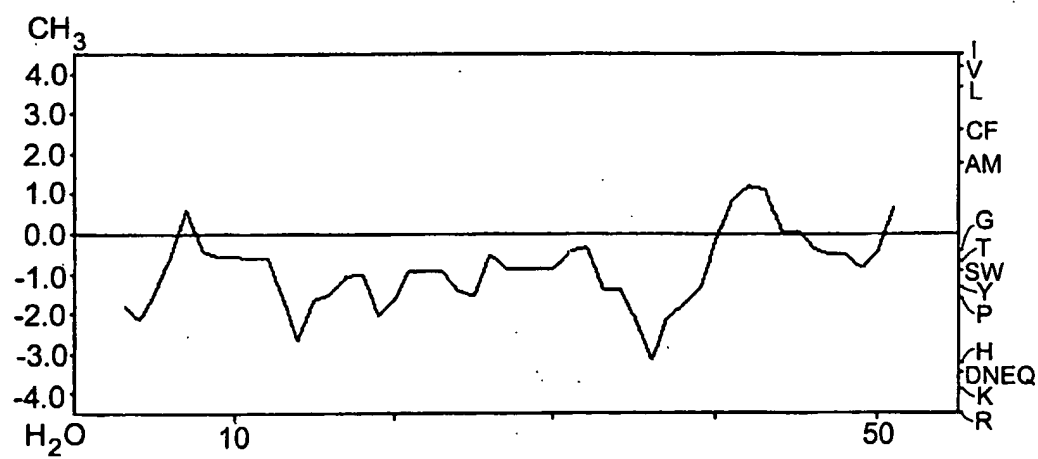


FIG. 11



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FIG. 12

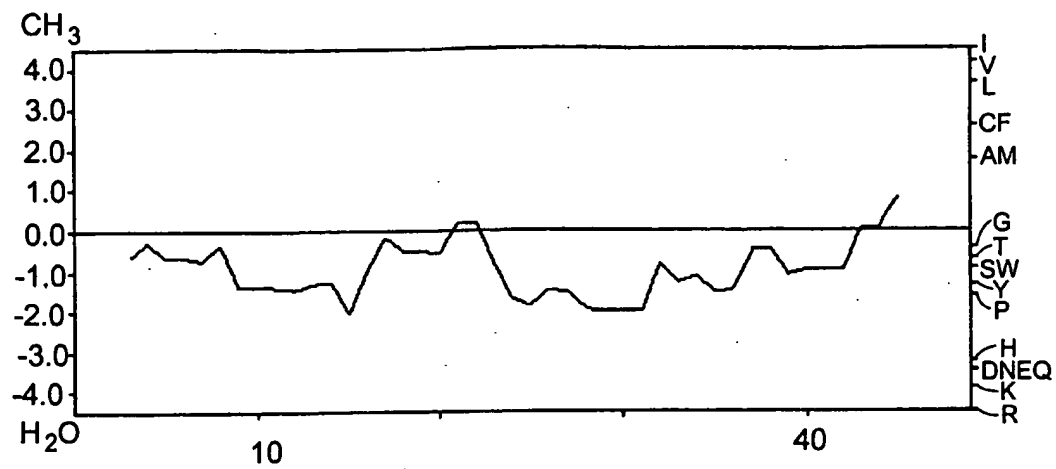
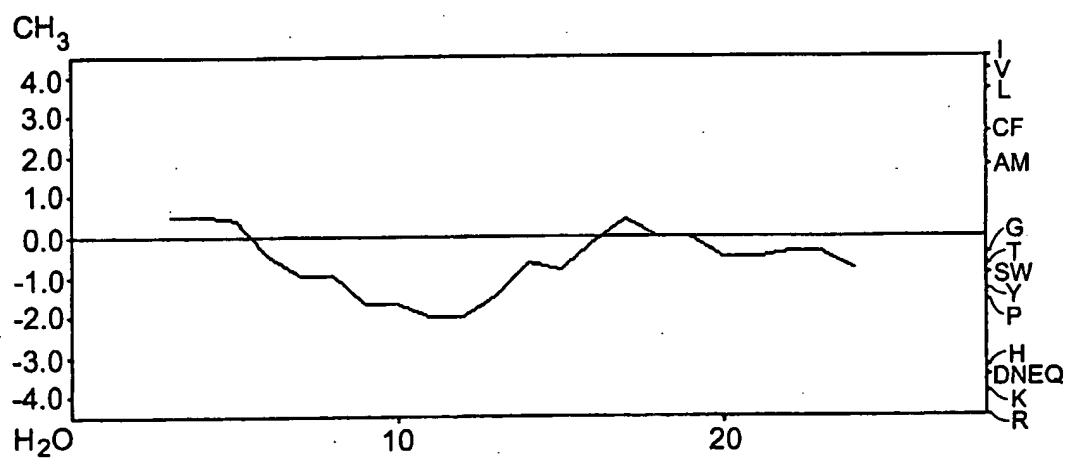


FIG. 13



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FIG. 14

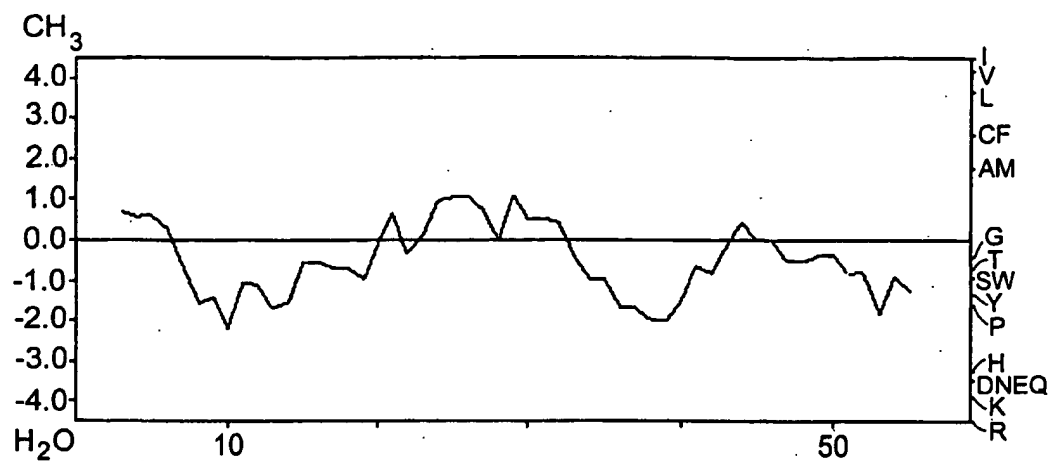
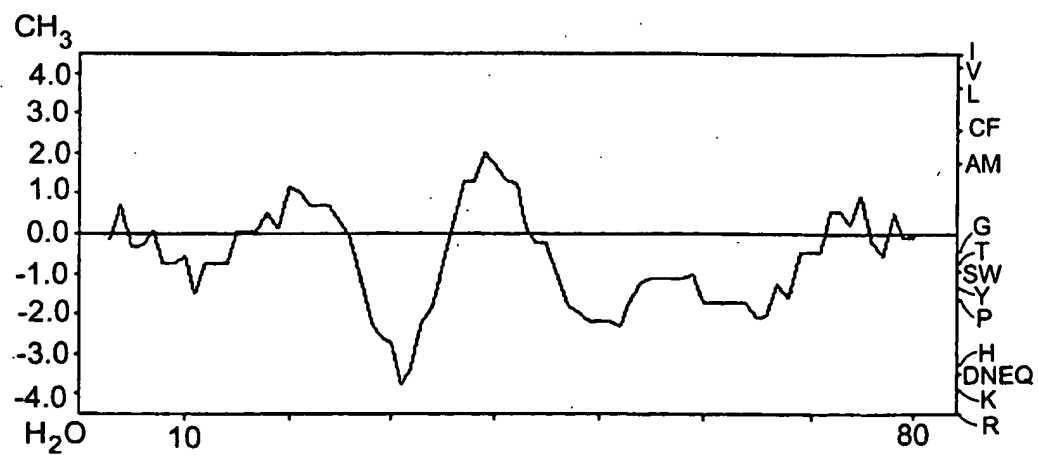


FIG. 15



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FIG. 16

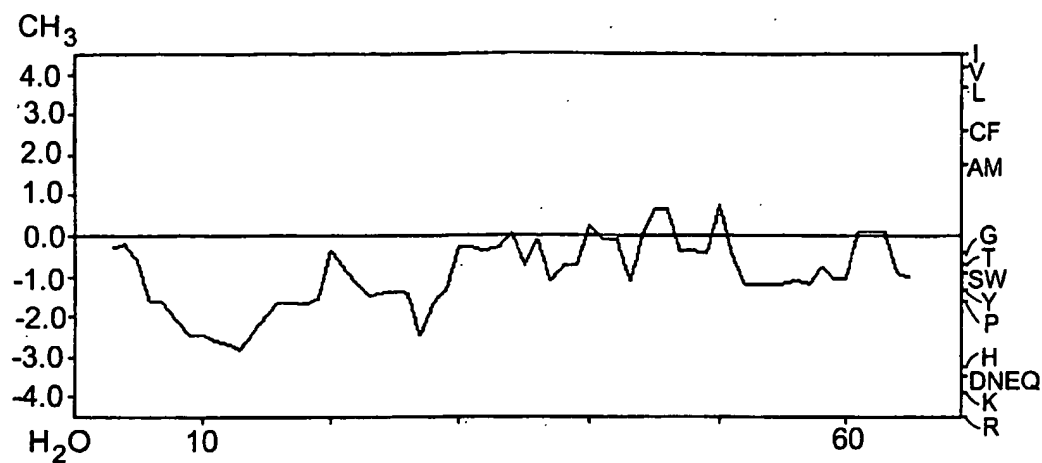
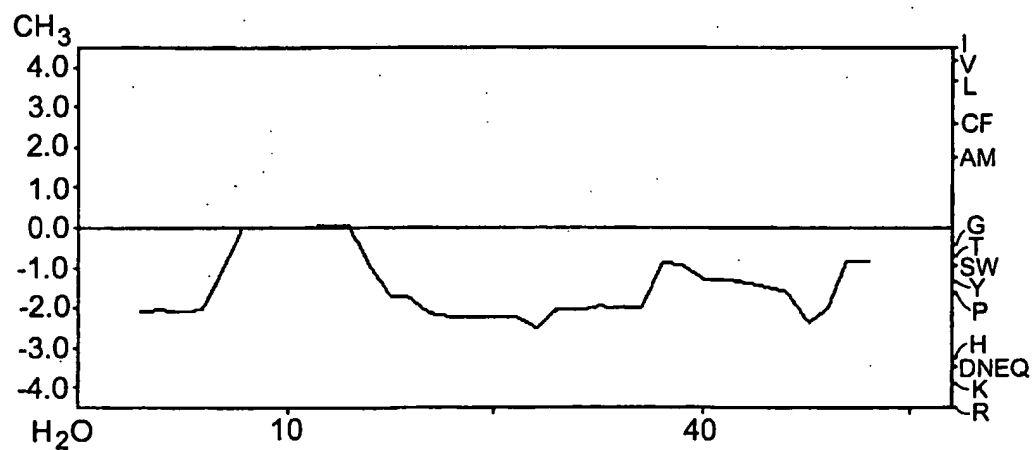


FIG. 17



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FIG. 18

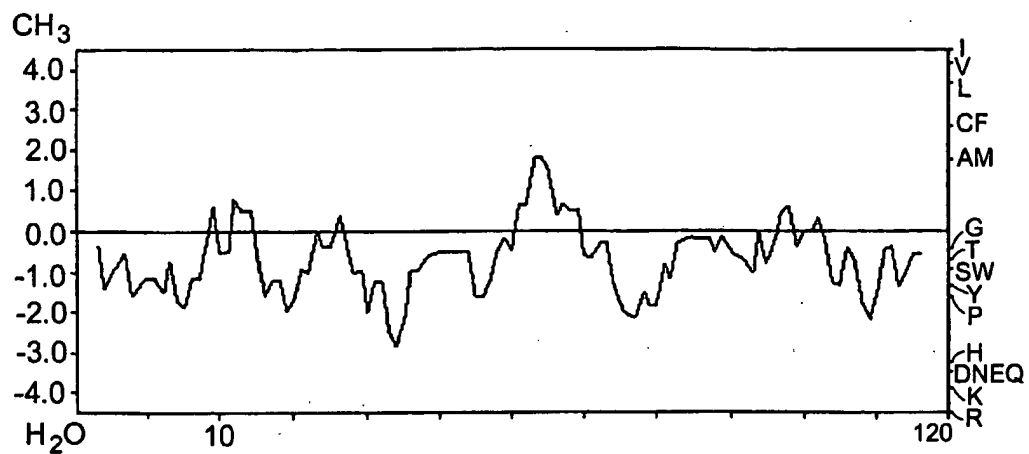
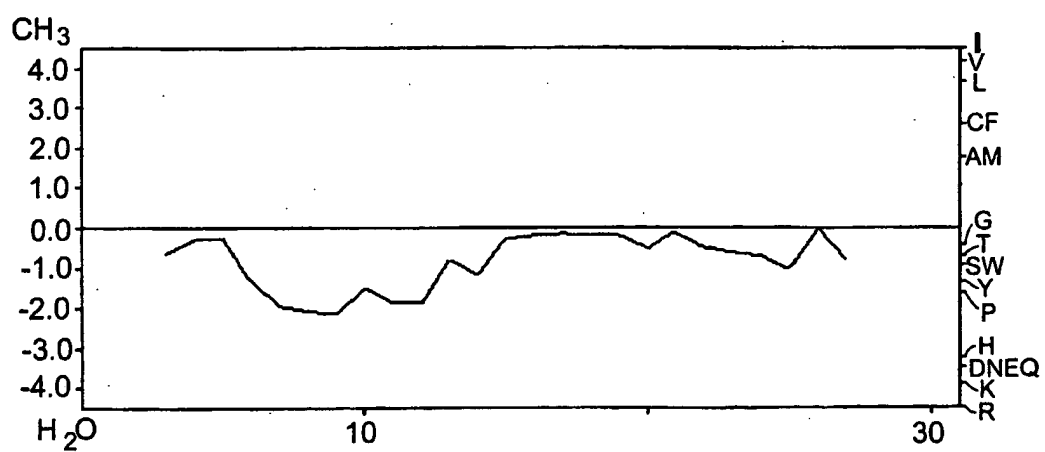


FIG. 19



## SEQUENCE LISTING

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KOVESDI, IMRE

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 Gly Asp Tyr Thr Asp Tyr Asp Asn Asn Met Pro Gly Pro Lys Lys Val  
 20 25 30  
 Phe Cys Asn Met Asp Val Asn Gly Gly Gly Trp Thr Val Asp Gln His  
 35 40 45  
 Arg Glu Asp Gly Ser Leu Asp Phe Gln Arg Gly Trp Lys Glu Tyr Lys  
 50 55 60  
 Met Gly Phe Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe  
 65 70 75 80  
 Asp Phe Ala Asp Thr Ser Gln Arg Gln Tyr Met Leu Arg Asp Glu Leu  
 85 90 95  
 Met Asp Trp Glu Gly Asn Arg Ala Tyr Ser Gln Tyr Asp Arg Phe His  
 100 105 110  
 Asp Gly Asn Glu Lys Gln Asn Tyr Arg Leu Tyr Leu Lys Gly His Thr  
 115 120 125  
 Gly Thr Ala Gly Lys Gln Ser Ser Leu Asp Leu His Gly Ala Asp Phe  
 130 135 140  
 Ser Thr Lys Asp Ala Asp Asn Asp Asn Cys Met Cys Lys Cys Ala Leu  
 145 150 155 160  
 Met Leu Thr Gly Gly Trp Trp Phe Asp Ala Cys Gly Pro Ser Asn Leu  
 165 170 175  
 Asn Gly Met Phe Tyr Thr Ala Gly Gln Asn His Gly Lys Leu Asn Gly  
 180 185 190  
 Asp Lys Trp His Tyr Phe Lys Phe Pro Ala Tyr Ala Leu Glu Ala Arg  
 195 200 205  
 Arg Met Met Asp Glu Pro Leu Asp Phe  
 210 215

<210> 3  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 3

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Met Pro Glu Pro Lys Lys Val Phe Cys Asn Met Asp Val Asn Gly Gly
1      5      10      15
Gly Trp Thr Val Asp Gln His Arg Glu Asp Gly Ser Leu Asp Phe Gln
20      25      30
Arg Gly Trp Lys Glu Tyr Lys Met Gly Phe Gly Asn Pro Ser Gly Glu
35      40      45
Tyr Trp Leu Gly Asn Glu Phe Asp Phe Ala Asp Thr Ser Gln Arg Gln
50      55      60
Tyr Met Leu Arg Asp Glu Leu Met Asp Trp Glu Gly Asn Arg Ala Tyr
65      70      75      80
Ser Gln Tyr Asp Arg Phe His Asp Gly Asn Glu Lys Gln Asn Tyr Arg
85      90      95
Leu Tyr Leu Lys Gly His Thr Gly Thr Ala Gly Lys Gln Ser Ser Leu
100     105
Asp Leu His Gly Ala Asp Phe Ser Thr Lys Asp Ala Asp Asn Asp Asn
115     120     125
Cys Met Cys Lys Cys Ala Leu Met Leu Thr Gly Gly Trp Trp Phe Asp
130     135     140
Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Phe Tyr Thr Ala Gly Gln
145     150     155     160
Asn His Gly Lys Leu Asn Gly Asp Lys Trp His Tyr Phe Lys Gly Pro
165     170     175
Ser Tyr Ser Leu Arg Ser Thr Thr Met Met Asp Arg Pro Leu Asp Phe
180     185     190

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<210> 4  
 <211> 207  
 <212> PRT  
 <213> Homo sapiens

<400> 4

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Arg Glu Ser Thr Thr Asp Gln Tyr Asn Thr Asn Ala Leu Gln Arg Asp
1      5      10      15
Ala Pro His Val Glu Pro Asp Phe Ser Ser Gln Lys Leu Gln His Leu
20      25      30
Glu His Val Met Glu Asn Tyr Thr Gln Trp Leu Gln Lys Leu Glu Asn
35      40      45
Tyr Asp Val Glu Asn Met Lys Ser Glu Met Ala Gln Asp Gln Gln Asn
50      55      60
Ala Val Gln Asn His Thr Ala Thr Met Leu Glu Asp Gly Thr Ser Leu
65      70      75      80
Leu Ser Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val Glu Thr
85      90      95
Gln Val Leu Asn Gln Thr Ser Arg Leu Glu Asp Gln Leu Leu Glu Asn
100     105
Ser Leu Ser Thr Tyr Lys Leu Glu Lys Gln Leu Leu Gln Gln Thr Asn
115     120     125
Glu Asp Leu Lys Asp His Glu Lys Asn Ser Leu Leu Glu His Lys Asp
130     135     140
Leu Glu Met Glu Gly Lys His Lys Glu Glu Leu Asp Thr Leu Lys Glu
145     150     155     160
Glu Lys Glu Asn Leu Gln Gly Leu Val Thr Arg Gln Thr Tyr Asp Asp
165     170     175
Gln Gln Leu Glu Lys Gln Leu Asn Arg Ala Thr Thr Asn Asn Ser Val

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                180                185                190
Leu Gln Lys Gln Gln Leu Glu Leu Met Asp Thr Val His Asn Leu
      195      200      205

<210> 5
<211> 644
<212> PRT
<213> Homo sapiens

<400> 5

Met Phe Ser Met Arg Ile Val Cys Leu Val Leu Ser Val Val Gly Thr
 1      5      10      15
Ala Trp Thr Ala Asp Ser Gly Glu Gly Asp Phe Leu Ala Glu Gly Gly
      20      25      30
Gly Val Arg Gly Pro Arg Val Val Glu Arg His Gln Ser Ala Cys Lys
      35      40      45
Asp Ser Asp Trp Pro Phe Cys Ser Asp Glu Asp Trp Asn Tyr Lys Cys
      50      55      60
Pro Ser Gly Cys Arg Met Lys Gly Leu Ile Asp Glu Val Asn Gln Asp
      65      70      75      80
Phe Thr Asn Arg Ile Asn Lys Leu Lys Asn Ser Leu Phe Glu Tyr Gln
      85      90      95
Lys Asn Asn Lys Asp Ser His Ser Leu Thr Thr Asn Ile Met Glu Ile
      100      105      110
Leu Arg Gly Asp Phe Ser Ser Ala Asn Asn Arg Asp Asn Thr Tyr Asn
      115      120      125
Arg Val Ser Glu Asp Leu Arg Ser Arg Ile Glu Val Leu Lys Arg Lys
      130      135      140
Val Ile Glu Lys Val Gln His Ile Gln Leu Leu Gln Lys Asn Val Arg
      145      150      155      160
Ala Gln Leu Val Asp Met Lys Arg Leu Glu Val Asp Ile Asp Ile Lys
      165      170      175
Ile Arg Ser Cys Arg Gly Ser Cys Ser Arg Ala Leu Ala Arg Glu Val
      180      185      190
Asp Leu Lys Asp Tyr Glu Asp Gln Gln Lys Gln Leu Glu Gln Val Ile
      195      200      205
Ala Lys Asp Leu Leu Pro Ser Arg Asp Arg Gln His Leu Pro Leu Ile
      210      215      220
Lys Met Lys Pro Val Pro Asp Leu Val Pro Gly Asn Phe Lys Ser Gln
      225      230      235      240
Leu Gln Lys Val Pro Pro Glu Trp Lys Ala Leu Thr Asp Met Pro Gln
      245      250      255
Met Arg Met Glu Leu Glu Arg Pro Gly Gly Asn Glu Ile Thr Arg Gly
      260      265      270
Gly Ser Thr Ser Tyr Gly Thr Gly Ser Glu Thr Glu Ser Pro Arg Asn
      275      280      285
Pro Ser Ser Ala Gly Ser Trp Asn Ser Gly Ser Ser Gly Pro Gly Ser
      290      295      300
Thr Gly Asn Arg Asn Pro Gly Ser Ser Gly Thr Gly Gly Thr Ala Thr
      305      310      315      320
Trp Lys Pro Gly Ser Ser Gly Pro Gly Ser Thr Gly Ser Trp Asn Ser
      325      330      335
Gly Ser Ser Gly Thr Gly Ser Thr Gly Asn Gln Asn Pro Gly Ser Pro
      340      345      350
Arg Pro Gly Ser Thr Gly Thr Trp Asn Pro Gly Ser Ser Glu Arg Gly
      355      360      365
Ser Ala Gly His Trp Thr Ser Glu Ser Ser Val Ser Gly Ser Thr Gly
      370      375      380

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Gln Trp His Ser Glu Ser Gly Ser Phe Arg Pro Asp Ser Pro Gly Ser  
 385 390 395 400  
 Gly Asn Ala Arg Pro Asn Asn Pro Asp Trp Gly Thr Phe Glu Glu Val  
 405 410 415  
 Ser Gly Asn Val Ser Pro Gly Thr Arg Arg Glu Tyr His Thr Glu Lys  
 420 425 430  
 Leu Val Thr Ser Lys Gly Asp Lys Glu Leu Arg Thr Gly Lys Glu Lys  
 435 440 445  
 Val Thr Ser Gly Ser Thr Thr Thr Thr Arg Arg Ser Cys Ser Lys Thr  
 450 455 460  
 Val Thr Lys Thr Val Ile Gly Pro Asp Gly His Lys Glu Val Thr Lys  
 465 470 475 480  
 Glu Val Val Thr Ser Glu Asp Gly Ser Asp Cys Pro Glu Ala Met Asp  
 485 490 495  
 Leu Gly Thr Leu Ser Gly Ile Gly Thr Leu Asp Gly Phe Arg His Arg  
 500 505 510  
 His Pro Asp Glu Ala Ala Phe Phe Asp Thr Ala Ser Thr Gly Lys Thr  
 515 520 525  
 Phe Pro Gly Phe Phe Ser Pro Met Leu Gly Glu Phe Val Ser Glu Thr  
 530 535 540  
 Glu Ser Arg Gly Ser Glu Ser Gly Ile Phe Thr Asn Thr Lys Glu Ser  
 545 550 555 560  
 Ser Ser His His Pro Gly Ile Ala Glu Phe Pro Ser Arg Gly Lys Ser  
 565 570 575  
 Ser Ser Tyr Ser Lys Gln Phe Thr Ser Ser Thr Ser Tyr Asn Arg Gly  
 580 585 590  
 Asp Ser Thr Phe Glu Ser Lys Ser Tyr Lys Met Ala Asp Glu Ala Gly  
 595 600 605  
 Ser Glu Ala Asp His Glu Gly Thr His Ser Thr Lys Arg Gly His Ala  
 610 615 620  
 Lys Ser Arg Pro Val Arg Gly Ile His Thr Ser Pro Leu Gly Lys Pro  
 625 630 635 640  
 Ser Leu Ser Pro

<210> 6  
 <211> 866  
 <212> PRT  
 <213> Homo sapiens

<400> 6

Met Phe Ser Met Arg Asp Val Cys Leu Val Leu Ser Val Val Gly Thr  
 1 5 10 15  
 Ala Trp Thr Ala Asp Ser Gly Glu Gly Asp Phe Leu Ala Glu Gly Gly  
 20 25 30  
 Gly Val Arg Gly Pro Arg Val Val Glu Arg His Gln Ser Ala Cys Lys  
 35 40 45  
 Asp Ser Asp Trp Pro Phe Cys Ser Asp Glu Asp Trp Asn Tyr Lys Cys  
 50 55 60  
 Pro Ser Gly Cys Arg Met Lys Gly Leu Asp Asp Glu Val Asn Gln Asp  
 65 70 75 80  
 Phe Thr Asn Arg Asp Asn Lys Leu Lys Asn Ser Leu Phe Glu Tyr Gln  
 85 90 95  
 Lys Asn Asn Lys Asp Ser His Ser Leu Thr Thr Asn Asp Met Glu Asp  
 100 105 110  
 Leu Arg Gly Asp Phe Ser Ser Ala Asn Asn Arg Asp Asn Thr Tyr Asn  
 115 120 125  
 Arg Val Ser Glu Asp Leu Arg Ser Arg Asp Glu Val Leu Lys Arg Lys  
 130 135 140

Val Asp Glu Lys Val Gln His Asp Gln Leu Leu Gln Lys Asn Val Arg  
 145 150 155 160  
 Ala Gln Leu Val Asp Met Lys Arg Leu Glu Val Asp Asp Asp Lys  
 165 170 175  
 Asp Arg Ser Cys Arg Gly Ser Cys Ser Arg Ala Leu Ala Arg Glu Val  
 180 185 190  
 Asp Leu Lys Asp Tyr Glu Asp Gln Gln Lys Gln Leu Glu Gln Val Asp  
 195 200 205  
 Ala Lys Asp Leu Leu Pro Ser Arg Asp Arg Gln His Leu Pro Leu Asp  
 210 215 220  
 Lys Met Lys Pro Val Pro Asp Leu Val Pro Gly Asn Phe Lys Ser Gln  
 225 230 235 240  
 Leu Gln Lys Val Pro Pro Glu Trp Lys Ala Leu Thr Asp Met Pro Gln  
 245 250 255  
 Met Arg Met Glu Leu Glu Arg Pro Gly Gly Asn Glu Asp Thr Arg Gly  
 260 265 270  
 Gly Ser Thr Ser Tyr Gly Thr Gly Ser Glu Thr Glu Ser Pro Arg Asn  
 275 280 285  
 Pro Ser Ser Ala Gly Ser Trp Asn Ser Gly Ser Ser Gly Pro Gly Ser  
 290 295 300  
 Thr Gly Asn Arg Asn Pro Gly Ser Ser Gly Thr Gly Gly Thr Ala Thr  
 305 310 315 320  
 Trp Lys Pro Gly Ser Ser Gly Pro Gly Ser Thr Gly Ser Trp Asn Ser  
 325 330 335  
 Gly Ser Ser Gly Thr Gly Ser Thr Gly Asn Gln Asn Pro Gly Ser Pro  
 340 345 350  
 Arg Pro Gly Ser Thr Gly Thr Trp Asn Pro Gly Ser Ser Glu Arg Gly  
 355 360 365  
 Ser Ala Gly His Trp Thr Ser Glu Ser Ser Val Ser Gly Ser Thr Gly  
 370 375 380  
 Gln Trp His Ser Glu Ser Gly Ser Phe Arg Pro Asp Ser Pro Gly Ser  
 385 390 395 400  
 Gly Asn Ala Arg Pro Asn Asn Pro Asp Trp Gly Thr Phe Glu Glu Val  
 405 410 415  
 Ser Gly Asn Val Ser Pro Gly Thr Arg Arg Glu Tyr His Thr Glu Lys  
 420 425 430  
 Leu Val Thr Ser Lys Gly Asp Lys Glu Leu Arg Thr Gly Lys Glu Lys  
 435 440 445  
 Val Thr Ser Gly Ser Thr Thr Thr Arg Arg Ser Cys Ser Lys Thr  
 450 455 460  
 Val Thr Lys Thr Val Asp Gly Pro Asp Gly His Lys Glu Val Thr Lys  
 465 470 475 480  
 Glu Val Val Thr Ser Glu Asp Gly Ser Asp Cys Pro Glu Ala Met Asp  
 485 490 495  
 Leu Gly Thr Leu Ser Gly Asp Gly Thr Leu Asp Gly Phe Arg His Arg  
 500 505 510  
 His Pro Asp Glu Ala Ala Phe Phe Asp Thr Ala Ser Thr Gly Lys Thr  
 515 520 525  
 Phe Pro Gly Phe Phe Ser Pro Met Leu Gly Glu Phe Val Ser Glu Thr  
 530 535 540  
 Glu Ser Arg Gly Ser Glu Ser Gly Asp Phe Thr Asn Thr Lys Glu Ser  
 545 550 555 560  
 Ser Ser His His Pro Gly Asp Ala Glu Phe Pro Ser Arg Gly Lys Ser  
 565 570 575  
 Ser Ser Tyr Ser Lys Gln Phe Thr Ser Thr Ser Tyr Asn Arg Gly  
 580 585 590

Asp Ser Thr Phe Glu Ser Lys Ser Tyr Lys Met Ala Asp Glu Ala Gly  
           595                  600          605  
 Ser Glu Ala Asp His Glu Gly Thr His Ser Thr Lys Arg Gly His Ala  
       610                  615          620  
 Lys Ser Arg Pro Val Arg Asp Cys Asp Asp Val Leu Gln Thr His Pro  
       625                  630          635          640  
 Ser Gly Thr Gln Ser Gly Asp Phe Asn Asp Lys Leu Pro Gly Ser Ser  
           645                  650          655  
 Lys Asp Phe Ser Val Tyr Cys Asp Gln Glu Thr Ser Leu Gly Gly Trp  
           660                  665          670  
 Leu Leu Asp Gln Gln Arg Met Asp Gly Ser Leu Asn Phe Asn Arg Thr  
           675                  680          685  
 Trp Gln Asp Tyr Lys Arg Gly Phe Gly Ser Leu Asn Asp Glu Gly Glu  
       690                  695          700  
 Gly Glu Phe Trp Leu Gly Asn Asp Tyr Leu His Leu Leu Thr Gln Arg  
       705                  710          715          720  
 Gly Ser Val Leu Arg Val Glu Leu Glu Asp Trp Ala Gly Asn Glu Ala  
           725                  730          735  
 Tyr Ala Glu Tyr His Phe Arg Val Gly Ser Glu Ala Glu Gly Tyr Ala  
           740                  745          750  
 Leu Gln Val Ser Ser Tyr Glu Gly Thr Ala Gly Asp Ala Leu Asp Glu  
       755                  760          765  
 Gly Ser Val Glu Glu Gly Ala Glu Tyr Thr Ser His Asn Asn Met Gln  
       770                  775          780  
 Phe Ser Thr Phe Asp Arg Asp Ala Asp Gln Trp Glu Glu Asn Cys Ala  
       785                  790          795          800  
 Glu Val Tyr Gly Gly Gly Trp Trp Tyr Asn Asn Cys Gln Ala Ala Asn  
           805                  810  
 Leu Asn Gly Asp Tyr Tyr Pro Gly Gly Ser Tyr Asp Pro Arg Asn Asn  
           820                  825          830  
 Ser Pro Tyr Glu Asp Glu Asn Gly Val Val Trp Val Ser Phe Arg Gly  
       835                  840          845  
 Ala Asp Tyr Ser Leu Arg Ala Val Arg Met Lys Asp Arg Pro Leu Val  
       850                  855          860

Thr Gln  
 865

<210> 7  
 <211> 491  
 <212> PRT  
 <213> Homo sapiens

<400> 7

Met Lys Arg Met Val Ser Trp Ser Phe His Lys Leu Lys Thr Met Lys  
       1                  5          10          15  
 His Leu Leu Leu Leu Leu Leu Cys Val Phe Leu Val Lys Ser Gln Gly  
           20                  25          30  
 Val Asn Asp Asn Glu Glu Gly Phe Phe Ser Ala Arg Gly His Arg Pro  
       35                  40          45  
 Leu Asp Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro  
       50                  55          60  
 Pro Asp Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala  
       65                  70          75          80  
 Thr Gln Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Cys Leu  
           85                  90          95  
 His Ala Asp Pro Asp Leu Gly Val Leu Cys Pro Thr Gly Cys Gln Leu  
           100                 105         110  
 Gln Glu Ala Leu Leu Gln Gln Glu Arg Pro Asp Arg Asn Ser Val Asp  
       115                 120         125

Glu Leu Asn Asn Asn Val Glu Ala Val Ser Gln Thr Ser Ser Ser Ser  
 130 135 140  
 Phe Gln Tyr Met Tyr Leu Leu Lys Asp Leu Trp Gln Lys Arg Gln Lys  
 145 150 155 160  
 Gln Val Lys Asp Asn Glu Asn Val Val Asn Glu Tyr Ser Ser Glu Leu  
 165 170 175  
 Glu Lys His Gln Leu Tyr Asp Asp Glu Thr Val Asn Ser Asn Asp Pro  
 180 185 190  
 Thr Asn Leu Arg Val Leu Arg Ser Asp Leu Glu Asn Leu Arg Ser Lys  
 195 200 205  
 Asp Gln Lys Leu Glu Ser Asp Val Ser Ala Gln Met Glu Tyr Cys Arg  
 210 215 220  
 Thr Pro Cys Thr Val Ser Cys Asn Asp Pro Val Val Ser Gly Lys Glu  
 225 230 235 240  
 Cys Glu Glu Asp Asp Arg Lys Gly Gly Glu Thr Ser Glu Met Tyr Leu  
 245 250 255  
 Asp Gln Pro Asp Ser Ser Val Lys Pro Tyr Arg Val Tyr Cys Asp Met  
 260 265 270  
 Asn Thr Glu Asn Gly Gly Trp Thr Val Asp Gln Asn Arg Gln Asp Gly  
 275 280 285  
 Ser Val Asp Phe Gly Arg Lys Trp Asp Pro Tyr Lys Gln Gly Phe Gly  
 290 295 300  
 Asn Val Ala Thr Asn Thr Asp Gly Lys Asn Tyr Cys Gly Leu Pro Gly  
 305 310 315 320  
 Glu Tyr Trp Leu Gly Asn Asp Lys Asp Ser Gln Leu Thr Arg Met Gly  
 325 330 335  
 Pro Thr Glu Leu Leu Asp Glu Met Glu Asp Trp Lys Gly Asp Lys Val  
 340 345 350  
 Lys Ala His Tyr Gly Gly Phe Thr Val Gln Asn Glu Ala Asn Lys Tyr  
 355 360 365  
 Gln Asp Ser Val Asn Lys Tyr Arg Gly Thr Ala Gly Asn Ala Leu Met  
 370 375 380  
 Asp Gly Ala Ser Gln Leu Met Gly Glu Asn Arg Thr Met Thr Asp His  
 385 390 395 400  
 Asn Gly Met Phe Phe Ser Thr Tyr Asp Arg Asp Asn Asp Gly Trp Leu  
 405 410 415  
 Thr Ser Asp Pro Arg Lys Gln Cys Ser Lys Glu Asp Gly Gly Gly Trp  
 420 425 430  
 Trp Tyr Asn Arg Cys His Ala Ala Asn Pro Asn Gly Arg Tyr Tyr Trp  
 435 440 445  
 Gly Gly Gln Tyr Thr Trp Asp Met Ala Lys His Gly Thr Asp Asp Gly  
 450 455 460  
 Val Val Trp Met Asn Trp Lys Gly Ser Trp Tyr Ser Met Arg Lys Met  
 465 470 475 480  
 Ser Met Lys Asp Arg Pro Phe Phe Pro Gln Gln  
 485 490

<210> 8  
 <211> 491  
 <212> PRT  
 <213> Homo sapiens

<400> 8

Met Lys Arg Met Val Ser Trp Ser Phe His Lys Leu Lys Thr Met Lys  
 1 5 10 15  
 His Leu Leu Leu Leu Leu Cys Val Phe Leu Val Lys Ser Gln Gly  
 20 25 30  
 Val Asn Asp Asn Glu Glu Gly Phe Phe Ser Ala Arg Gly His Arg Pro

35					40					45					
Leu	Asp	Lys	Lys	Arg	Glu	Glu	Ala	Pro	Ser	Leu	Arg	Pro	Ala	Pro	Pro
50					55					60					
Pro	Asp	Ser	Gly	Gly	Gly	Tyr	Arg	Ala	Arg	Pro	Ala	Lys	Ala	Ala	Ala
65					70					75					80
Thr	Gln	Lys	Lys	Val	Glu	Arg	Lys	Ala	Pro	Asp	Ala	Gly	Gly	Cys	Leu
				85					90					95	
His	Ala	Asp	Pro	Asp	Leu	Gly	Val	Leu	Cys	Pro	Thr	Gly	Cys	Gln	Leu
			100					105					110		
Gln	Glu	Ala	Leu	Leu	Gln	Gln	Glu	Arg	Pro	Asp	Arg	Asn	Ser	Val	Asp
		115					120					125			
Glu	Leu	Asn	Asn	Asn	Val	Glu	Ala	Val	Ser	Gln	Thr	Ser	Ser	Ser	Ser
	130					135					140				
Phe	Gln	Tyr	Met	Tyr	Leu	Leu	Lys	Asp	Leu	Trp	Gln	Lys	Arg	Gln	Lys
145					150					155					160
Gln	Val	Lys	Asp	Asn	Glu	Asn	Val	Val	Asn	Glu	Tyr	Ser	Ser	Glu	Leu
				165					170					175	
Glu	Lys	His	Gln	Leu	Tyr	Asp	Asp	Glu	Thr	Val	Asn	Ser	Asn	Asp	Pro
			180					185					190		
Thr	Asn	Leu	Arg	Val	Leu	Arg	Ser	Asp	Leu	Glu	Asn	Leu	Arg	Ser	Lys
			195				200					205			
Asp	Gln	Lys	Leu	Glu	Ser	Asp	Val	Ser	Ala	Gln	Met	Glu	Tyr	Cys	Arg
	210					215					220				
Thr	Pro	Cys	Thr	Val	Ser	Cys	Asn	Asp	Pro	Val	Val	Ser	Gly	Lys	Glu
225						230				235					240
Cys	Glu	Glu	Asp	Asp	Arg	Lys	Gly	Gly	Glu	Thr	Ser	Glu	Met	Tyr	Leu
				245					250					255	
Asp	Gln	Pro	Asp	Ser	Ser	Val	Lys	Pro	Tyr	Arg	Val	Tyr	Cys	Asp	Met
			260					265					270		
Asn	Thr	Glu	Asn	Gly	Gly	Trp	Thr	Val	Asp	Gln	Asn	Arg	Gln	Asp	Gly
		275					280					285			
Ser	Val	Asp	Phe	Gly	Arg	Lys	Trp	Asp	Pro	Tyr	Lys	Gln	Gly	Phe	Gly
		290				295					300				
Asn	Val	Ala	Thr	Asn	Thr	Asp	Gly	Lys	Asn	Tyr	Cys	Gly	Leu	Pro	Gly
				310							315				320
Glu	Tyr	Trp	Leu	Gly	Asn	Asp	Lys	Asp	Ser	Gln	Leu	Thr	Arg	Met	Gly
				325					330					335	
Pro	Thr	Glu	Leu	Leu	Asp	Glu	Met	Glu	Asp	Trp	Lys	Gly	Asp	Lys	Val
			340					345					350		
Lys	Ala	His	Tyr	Gly	Gly	Phe	Thr	Val	Gln	Asn	Glu	Ala	Asn	Lys	Tyr
		355					360					365			
Gln	Asp	Ser	Val	Asn	Lys	Tyr	Arg	Gly	Thr	Ala	Gly	Asn	Ala	Leu	Met
	370					375					380				
Asp	Gly	Ala	Ser	Gln	Leu	Met	Gly	Glu	Asn	Arg	Thr	Met	Thr	Asp	His
				390					395						400
Asn	Gly	Met	Phe	Phe	Ser	Thr	Tyr	Asp	Arg	Asp	Asn	Asp	Gly	Trp	Leu
				405					410					415	
Thr	Ser	Asp	Pro	Arg	Lys	Gln	Cys	Ser	Lys	Glu	Asp	Gly	Gly	Gly	Trp
			420					425					430		
Trp	Tyr	Asn	Arg	Cys	His	Ala	Ala	Asn	Pro	Asn	Gly	Arg	Tyr	Tyr	Trp
		435					440					445			
Gly	Gly	Gln	Tyr	Thr	Trp	Asp	Met	Ala	Lys	His	Gly	Thr	Asp	Asp	Gly
		450				455					460				
Val	Val	Trp	Met	Asn	Trp	Lys	Gly	Ser	Trp	Tyr	Ser	Met	Arg	Lys	Met
				470					475						480
Ser	Met	Lys	Asp	Arg	Pro	Phe	Phe	Pro	Gln	Gln					

485

490

<210> 9  
 <211> 437  
 <212> PRT  
 <213> Homo sapiens

<400> 9

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Met Ser Trp Ser Leu His Pro Arg Asn Leu Asp Leu Tyr Phe Tyr Ala
1      5      10      15
Leu Leu Phe Leu Ser Ser Thr Cys Val Ala Tyr Val Ala Thr Arg Asp
20      25      30
Asn Cys Cys Asp Leu Asp Glu Arg Phe Gly Ser Tyr Cys Pro Thr Thr
35      40      45
Cys Gly Asp Ala Asp Phe Leu Ser Thr Tyr Gln Thr Lys Val Asp Lys
50      55      60
Asp Leu Gln Ser Leu Glu Asp Asp Leu His Gln Val Glu Asn Lys Thr
65      70      75      80
Ser Glu Val Lys Gln Leu Asp Lys Ala Asp Gln Leu Thr Tyr Asn Pro
85      90      95
Asp Glu Ser Ser Lys Pro Asn Met Asp Asp Ala Ala Thr Leu Lys Ser
100     105     110
Arg Asp Met Leu Glu Glu Asp Met Lys Tyr Glu Ala Ser Asp Leu Thr
115     120     125
His Asp Ser Ser Asp Arg Tyr Leu Gln Glu Asp Tyr Asn Ser Asn Asn
130     135     140
Gln Lys Asp Val Asn Leu Lys Glu Lys Val Ala Gln Leu Glu Ala Gln
145     150     155     160
Cys Gln Glu Pro Cys Lys Asp Thr Val Gln Asp His Asp Asp Thr Gly
165     170     175
Lys Asp Cys Gln Asp Asp Ala Asn Lys Gly Ala Lys Gln Ser Gly Leu
180     185     190
Tyr Phe Asp Lys Pro Leu Lys Ala Asn Gln Gln Phe Leu Val Tyr Cys
195     200     205
Glu Asp Asp Gly Ser Gly Asn Gly Trp Thr Val Phe Gln Lys Arg Leu
210     215     220
Asp Gly Ser Val Asp Phe Lys Lys Asn Trp Asp Gln Tyr Lys Glu Gly
225     230     235     240
Phe Gly His Leu Ser Pro Thr Gly Thr Thr Glu Phe Trp Leu Gly Asn
245     250     255
Glu Lys Asp His Leu Asp Ser Thr Gln Ser Ala Asp Pro Tyr Ala Leu
260     265     270
Arg Val Glu Leu Glu Asp Trp Asn Gly Arg Thr Ser Thr Ala Asp Tyr
275     280     285
Ala Met Phe Lys Val Gly Pro Glu Ala Asp Lys Tyr Arg Leu Thr Tyr
290     295     300
Ala Tyr Phe Ala Gly Gly Asp Ala Gly Asp Ala Phe Asp Gly Phe Asp
305     310     315     320
Phe Gly Asp Asp Pro Ser Asp Lys Phe Phe Thr Ser His Asn Gly Met
325     330     335
Gln Phe Ser Thr Trp Asp Asn Asp Asn Asp Lys Phe Glu Gly Asn Cys
340     345     350
Ala Glu Gln Asp Gly Ser Gly Trp Trp Met Asn Lys Cys His Ala Gly
355     360     365
His Leu Asn Gly Val Tyr Tyr Gln Gly Gly Thr Tyr Ser Lys Ala Ser
370     375     380
Thr Pro Asn Gly Tyr Asp Asn Gly Asp Asp Trp Ala Thr Trp Lys Thr
385     390     395     400

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Arg Trp Tyr Ser Met Lys Lys Thr Thr Met Lys Asp Asp Pro Phe Asn  
 405 410 415  
 Arg Leu Thr Asp Gly Glu Gly Gln Gln His His Leu Gly Gly Ala Lys  
 420 425 430  
 Gln Ala Gly Asp Val  
 435  
 <210> 10  
 <211> 453  
 <212> PRT  
 <213> Homo sapiens  
 <400> 10  
 Met Ser Trp Ser Leu His Pro Arg Asn Leu Asp Leu Tyr Phe Tyr Ala  
 1 5 10 15  
 Leu Leu Phe Leu Ser Ser Thr Cys Val Ala Tyr Val Ala Thr Arg Asp  
 20 25 30  
 Asn Cys Cys Asp Leu Asp Glu Arg Phe Gly Ser Tyr Cys Pro Thr Thr  
 35 40 45  
 Cys Gly Asp Ala Asp Phe Leu Ser Thr Tyr Gln Thr Lys Val Asp Lys  
 50 55 60  
 Asp Leu Gln Ser Leu Glu Asp Asp Leu His Gln Val Glu Asn Lys Thr  
 65 70 75 80  
 Ser Glu Val Lys Gln Leu Asp Lys Ala Asp Gln Leu Thr Tyr Asn Pro  
 85 90 95  
 Asp Glu Ser Ser Lys Pro Asn Met Asp Asp Ala Ala Thr Leu Lys Ser  
 100 105 110  
 Arg Lys Met Leu Glu Glu Asp Met Lys Tyr Glu Ala Ser Asp Leu Thr  
 115 120 125  
 His Asp Ser Ser Asp Arg Tyr Leu Gln Glu Asp Tyr Asn Ser Asn Asn  
 130 135 140  
 Gln Lys Asp Val Asn Leu Lys Glu Lys Val Ala Gln Leu Glu Ala Gln  
 145 150 155 160  
 Cys Gln Glu Pro Cys Lys Asp Thr Val Gln Asp His Asp Asp Thr Gly  
 165 170 175  
 Lys Asp Cys Gln Asp Asp Ala Asn Lys Gly Ala Lys Gln Ser Gly Leu  
 180 185 190  
 Tyr Phe Asp Lys Pro Leu Lys Ala Asn Gln Gln Phe Leu Val Tyr Cys  
 195 200 205  
 Glu Asp Asp Gly Ser Gly Asn Gly Trp Thr Val Phe Gln Lys Arg Leu  
 210 215 220  
 Asp Gly Ser Val Asp Phe Lys Lys Asn Trp Asp Gln Tyr Lys Glu Gly  
 225 230 235 240  
 Phe Gly His Leu Ser Pro Thr Gly Thr Thr Glu Phe Trp Leu Gly Asn  
 245 250 255  
 Glu Lys Asp His Leu Asp Ser Thr Gln Ser Ala Asp Pro Tyr Ala Leu  
 260 265 270  
 Arg Val Glu Leu Glu Asp Trp Asn Gly Arg Thr Ser Thr Ala Asp Tyr  
 275 280 285  
 Ala Met Phe Lys Val Gly Pro Glu Ala Asp Lys Tyr Arg Leu Thr Tyr  
 290 295 300  
 Ala Tyr Phe Ala Gly Gly Asp Ala Gly Asp Ala Phe Asp Gly Phe Asp  
 305 310 315 320  
 Phe Gly Asp Asp Pro Ser Asp Lys Phe Phe Thr Ser His Asn Gly Met  
 325 330 335  
 Gln Phe Ser Thr Trp Asp Asn Asp Asn Asp Lys Phe Glu Gly Asn Cys  
 340 345 350  
 Ala Glu Gln Asp Gly Ser Gly Trp Trp Met Asn Lys Cys His Ala Gly  
 355 360 365



His Leu Asn Gly Val Tyr Tyr Gln Gly Gly Thr Tyr Ser Lys Ala Ser  
 370 375 380  
 Thr Pro Asn Gly Tyr Asp Asn Gly Asp Asp Trp Ala Thr Trp Lys Thr  
 385 390 395 400  
 Arg Trp Tyr Ser Met Lys Lys Thr Thr Met Lys Asp Asp Pro Phe Asn  
 405 410 415  
 Arg Leu Thr Asp Gly Glu Gly Gln Gln His His Leu Gly Gly Ala Lys  
 420 425 430  
 Gln Val Arg Pro Glu His Pro Ala Glu Thr Glu Tyr Asp Ser Leu Tyr  
 435 440 445  
 Pro Glu Asp Asp Leu  
 450

<210> 11  
 <211> 221  
 <212> PRT  
 <213> Homo sapiens

<400> 11

Glu Glu Gln Asp Ser Phe Arg Asp Cys Ala Glu Val Phe Lys Ser Gly  
 1 5 10 15  
 His Thr Thr Asn Gly Asp Tyr Thr Leu Thr Phe Pro Asn Ser Thr Glu  
 20 25 30  
 Glu Asp Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly Gly Gly Trp Thr  
 35 40 45  
 Asp Asp Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln Arg Thr Trp  
 50 55 60  
 Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu Tyr Trp Leu  
 65 70 75 80  
 Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg Tyr Val Leu  
 85 90 95  
 Lys Asp His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr Ser Leu Tyr  
 100 105 110  
 Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg Asp His Leu  
 115 120 125  
 Lys Gly Leu Thr Gly Thr Ala Gly Lys Asp Ser Ser Asp Ser Gln Pro  
 130 135 140  
 Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys Cys Asp Cys  
 145 150 155 160  
 Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp Ala Cys Gly  
 165 170 175  
 Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln Asn Thr Asn  
 180 185 190  
 Lys Phe Asn Gly Asp Lys Trp Tyr Tyr Trp Lys Gly Ser Gly Tyr Ser  
 195 200 205  
 Leu Lys Ala Thr Thr Met Met Asp Arg Pro Ala Asp Phe  
 210 215 220

<210> 12  
 <211> 216  
 <212> PRT  
 <213> Homo sapiens

<400> 12

Phe Gln Asp Cys Ala Glu Asp Lys Arg Ser Gly Val Asn Thr Ser Gly  
 1 5 10 15  
 Val Tyr Thr Asp Tyr Glu Thr Asn Met Thr Lys Pro Leu Lys Val Phe  
 20 25 30  
 Cys Asp Met Glu Thr Asp Gly Gly Gly Trp Thr Leu Asp Gln His Arg  
 35 40 45

Glu Asp Gly Ser Val Asn Phe Gln Arg Thr Trp Glu Glu Tyr Lys Glu  
 50 55 60  
 Gly Phe Gly Asn Val Ala Arg Glu His Trp Leu Gly Asn Glu Ala Val  
 65 70 75 80  
 His Arg Leu Thr Ser Arg Thr Ala Tyr Leu Arg Val Glu Leu His  
 85 90 95  
 Asp Trp Glu Gly Arg Gln Thr Ser Asp Gln Tyr Glu Asn Phe Gln Leu  
 100 105 110  
 Gly Ser Glu Arg Gln Arg Tyr Ser Leu Ser Val Asn Asp Ser Ser Ser  
 115 120 125  
 Ser Ala Gly Arg Lys Asn Ser Leu Ala Pro Gln Gly Thr Lys Phe Ser  
 130 135 140  
 Thr Lys Asp Met Asp Asn Asp Asn Cys Met Cys Lys Cys Ala Gln Met  
 145 150 155 160  
 Leu Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly Leu Ser Asn Leu Asn  
 165 170 175  
 Gly Asp Tyr Tyr Ser Val His Gln His Leu His Lys Asp Asn Gly Asp  
 180 185 190  
 Arg Trp His Tyr Phe Arg Gly Pro Ser Tyr Ser Leu His Gly Thr Arg  
 195 200 205  
 Met Met Leu Arg Pro Met Gly Ala  
 210 215

<210> 13  
 <211> 216  
 <212> PRT  
 <213> Homo sapiens

<400> 13

Phe Gln Asp Cys Ala Glu Asp Gln Arg Ser Gly Ala Ser Ala Ser Gly  
 1 5 10 15  
 Val Tyr Thr Asp Gln Val Ser Asn Ala Thr Lys Pro Arg Lys Val Phe  
 20 25 30  
 Cys Asp Leu Gln Ser Ser Gly Gly Arg Trp Thr Leu Asp Gln Arg Arg  
 35 40 45  
 Glu Asn Gly Thr Val Asn Phe Gln Arg Asn Trp Lys Asp Tyr Lys Gln  
 50 55 60  
 Gly Phe Gly Asp Pro Ala Gly Glu His Trp Leu Gly Asn Glu Val Val  
 65 70 75 80  
 His Gln Leu Thr Arg Arg Ala Ala Tyr Ser Leu Arg Val Glu Leu Gln  
 85 90 95  
 Asp Trp Glu Gly His Glu Ala Tyr Ala Gln Tyr Glu His Phe His Leu  
 100 105 110  
 Gly Ser Glu Asn Gln Leu Tyr Arg Leu Ser Val Val Gly Tyr Ser Gly  
 115 120 125  
 Ser Ala Gly Arg Gln Ser Ser Leu Val Leu Gln Asn Thr Ser Phe Ser  
 130 135 140  
 Thr Leu Asp Ser Asp Asn Asp His Cys Leu Cys Lys Cys Ala Gln Val  
 145 150 155 160  
 Met Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly Leu Ser Asn Leu Asn  
 165 170 175  
 Gly Val Tyr Tyr His Ala Pro Asp Asn Lys Tyr Lys Met Asp Gly Asp  
 180 185 190  
 Arg Trp His Tyr Phe Lys Gly Pro Ser Tyr Ser Leu Arg Ala Ser Arg  
 195 200 205  
 Met Met Asp Arg Pro Leu Asp Asp  
 210 215

<210> 14  
 <211> 224

<212> PRT  
<213> Homo sapiens

<400> 14

Lys Pro Ser Gly Pro Trp Arg Asp Cys Leu Gln Ala Leu Glu Asp Gly  
1 5 10 15  
His Asp Thr Ser Ser Asp Tyr Leu Val Lys Pro Glu Asn Thr Asn Arg  
20 25 30  
Leu Met Gln Val Trp Cys Asp Gln Arg His Asp Pro Gly Gly Trp Thr  
35 40 45  
Val Asp Gln Arg Arg Leu Asp Gly Ser Val Asn Phe Arg Asn Trp  
50 55 60  
Glu Thr Tyr Lys Gln Gly Phe Gly Asn Asp Asp Gly Glu Tyr Trp Leu  
65 70 75 80  
Gly Leu Glu Asn Asp Tyr Trp Leu Thr Asn Gln Gly Asn Tyr Lys Leu  
85 90 95  
Leu Val Thr Met Glu Asp Trp Ser Gly Arg Lys Val Phe Ala Glu Tyr  
100 105 110  
Ala Ser Phe Arg Leu Glu Pro Glu Ser Glu Tyr Tyr Lys Leu Arg Leu  
115 120 125  
Gly Arg Tyr His Gly Asn Ala Gly Asp Ser Phe Thr Trp His Asn Gly  
130 135 140  
Lys Gln Phe Thr Thr Leu Asp Arg Asp His Asp Val Tyr Thr Gly Asn  
145 150 155 160  
Cys Ala His Tyr Gln Lys Gly Gly Trp Trp Tyr Asn Ala Cys Ala His  
165 170 175  
Ser Asn Leu Asn Gly Val Trp Tyr Arg Gly Gly His Tyr Arg Ser Arg  
180 185 190  
Tyr Gln Asp Gly Val Tyr Trp Ala Glu Phe Arg Gly Gly Ser Tyr Ser  
195 200 205  
Leu Lys Lys Val Val Met Met Asp Arg Pro Asn Pro Asn Thr Phe His  
210 215 220

<210> 15  
<211> 219  
<212> PRT  
<213> Homo sapiens

<400> 15

Lys Met Gly Pro Lys Gly Glu Pro Gly Pro Arg Asn Cys Arg Glu Leu  
1 5 10 15  
Leu Ser Gln Gly Ala Thr Leu Ser Gly Trp Tyr His Leu Cys Leu Pro  
20 25 30  
Glu Gly Arg Ala Leu Pro Val Phe Cys Asp Met Asp Thr Glu Gly Gly  
35 40 45  
Gly Trp Leu Val Phe Gln Arg Arg Gln Asp Gly Ser Val Asp Phe Phe  
50 55 60  
Arg Ser Trp Ser Ser Tyr Arg Ala Gly Phe Gly Asn Gln Glu Ser Glu  
65 70 75 80  
Phe Trp Leu Gly Asn Glu Asn Leu His Gln Leu Thr Leu Gln Gly Asn  
85 90 95  
Trp Glu Leu Arg Val Glu Leu Glu Asp Phe Asn Gly Asn Arg Thr Phe  
100 105 110  
Ala His Tyr Ala Thr Phe Arg Leu Leu Gly Glu Val Asp His Tyr Gln  
115 120 125  
Leu Ala Leu Gly Lys Phe Ser Glu Gly Thr Ala Gly Asp Ser Leu Ser  
130 135 140  
Leu His Ser Gly Arg Pro Phe Thr Thr Tyr Asp Ala Asp His Asp Ser  
145 150 155 160

Ser Asn Ser Asn Cys Ala Val Asp Val His Gly Ala Trp Trp Tyr Ala  
 165 170 175  
 Ser Cys Tyr Arg Ser Asn Leu Asn Gly Arg Tyr Ala Val Ser Glu Ala  
 180 185 190  
 Ala Ala His Lys Tyr Gly Asp Asp Trp Ala Ser Gly Arg Gly Val Gly  
 195 200 205  
 His Pro Tyr Arg Arg Val Arg Met Met Leu Arg  
 210 215

<210> 16  
 <211> 217  
 <212> PRT  
 <213> Homo sapiens

<400> 16

Asp Cys Ser Ser Leu Tyr Gln Lys Asn Tyr Arg Asp Ser Gly Val Tyr  
 1 5 10 15  
 Lys Leu Pro Pro Asp Asp Phe Leu Gly Ser Pro Glu Leu Glu Val Phe  
 20 25 30  
 Cys Asp Met Glu Thr Ser Gly Gly Trp Thr Asp Asp Gln Arg Arg  
 35 40 45  
 Lys Ser Gly Leu Val Ser Phe Tyr Arg Asp Trp Lys Gln Tyr Lys Gln  
 50 55 60  
 Gly Phe Gly Ser Asp Arg Gly Asp Phe Trp Leu Gly Asn Glu His Asp  
 65 70 75 80  
 His Arg Leu Ser Arg Gln Pro Thr Arg Leu Arg Val Glu Met Glu Asp  
 85 90 95  
 Trp Glu Gly Asn Leu Arg Tyr Ala Glu Tyr Ser His Phe Val Leu Gly  
 100 105 110  
 Asn Glu Leu Asn Ser Tyr Arg Leu Phe Leu Gly Asn Tyr Thr Gly Asn  
 115 120 125  
 Val Gly Asn Asp Ala Leu Gln Tyr His Asn Asn Thr Ala Phe Ser Thr  
 130 135 140  
 Lys Asp Lys Asp Asn Asp Asn Cys Leu Asp Lys Cys Ala Gln Leu Arg  
 145 150 155 160  
 Lys Gly Gly Tyr Trp Tyr Asn Cys Cys Thr Asp Ser Asn Leu Asn Gly  
 165 170 175  
 Val Tyr Tyr Arg Leu Gly Glu His Asn Lys His Leu Asp Gly Asp Thr  
 180 185 190  
 Trp Tyr Gly Trp His Gly Ser Thr Tyr Ser Leu Lys Arg Val Glu Met  
 195 200 205  
 Lys Asp Arg Pro Glu Asp Phe Lys Pro  
 210 215

<210> 17  
 <211> 220  
 <212> PRT  
 <213> Homo sapiens

<400> 17

Asp Asn Glu Gly Pro Phe Lys Asp Cys Gln Gln Ala Lys Glu Ala Gly  
 1 5 10 15  
 His Ser Val Ser Gly Asp Tyr Met Asp Lys Pro Glu Asn Ser Asn Gly  
 20 25 30  
 Pro Met Gln Leu Trp Cys Glu Asn Ser Leu Asp Pro Gly Gly Trp Thr  
 35 40 45  
 Val Asp Gln Lys Arg Thr Asp Gly Ser Val Asn Phe Phe Arg Asn Trp  
 50 55 60  
 Glu Asn Tyr Lys Lys Gly Phe Gly Asn Asp Asp Gly Glu Tyr Trp Leu  
 65 70 75 80  
 Gly Leu Glu Asn Asp Tyr Met Leu Ser Asn Gln Asp Asn Tyr Lys Leu



His Thr Ser Gly Met Tyr Ala Asp Arg Pro Ser Asn Ser Gln Val Phe  
 20 25 30  
 His Val Tyr Cys Asp Val Asp Ser Gly Ser Pro Trp Thr Leu Asp Gln  
 35 40 45  
 His Arg Asp Asp Gly Ser Gln Asn Phe Asn Glu Thr Trp Glu Asn Tyr  
 50 55 60  
 Lys Tyr Gly Phe Gly Arg Leu Asp Gly Glu Phe Trp Leu Gly Leu Glu  
 65 70 75 80  
 Lys Asp Tyr Ser Asp Val Lys Gln Ser Asn Tyr Val Leu Arg Asp Glu  
 85 90 95  
 Leu Glu Asp Trp Lys Asp Asn Lys His Tyr Asp Glu Tyr Ser Phe Tyr  
 100 105 110  
 Leu Gly Asn His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Asp Thr  
 115 120 125  
 Gly Asn Val Pro Asn Ala Asp Pro Glu Asn Lys Asp Leu Val Phe Ser  
 130 135 140  
 Thr Trp Asp His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr  
 145 150 155 160  
 Ser Gly Gly Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn  
 165 170 175  
 Gly Lys Tyr Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg  
 180 185 190  
 Gly Leu Ser Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Asp Lys Ser  
 195 200 205  
 Thr Lys Met Leu Asp His Pro Thr Asp Ser Glu Ser Phe Glu  
 210 215 220

<210> 20  
 <211> 184  
 <212> PRT  
 <213> Homo sapiens

<400> 20

His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe Gln Val Gly Glu Arg  
 1 5 10 15  
 Gln Ser Gly Leu Phe Glu Asp Gln Pro Gln Gly Ser Pro Pro Phe Leu  
 20 25 30  
 Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp Thr Val Asp Gln Arg  
 35 40 45  
 Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro Trp Glu Ala Tyr Lys  
 50 55 60  
 Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp Leu Gly Leu Glu Lys  
 65 70 75 80  
 Val His Ser Asp Met Gly Asp Arg Asn Ser Arg Leu Ala Val Gln Leu  
 85 90 95  
 Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln Phe Ser Val His Leu  
 100 105 110  
 Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu Thr Ala Pro Val Ala  
 115 120 125  
 Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser Gly Leu Ser Val Pro  
 130 135 140  
 Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg Arg Asp Lys Asn Cys  
 145 150 155 160  
 Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly Thr Cys Ser His Ser  
 165 170 175  
 Asn Leu Asn Gly Gln Tyr Phe Arg  
 180

<210> 21

<211> 214  
 <212> PRT  
 <213> Homo sapiens

<400> 21

Arg Asp Cys Gln Glu Leu Phe Gln Glu Gly Glu Arg His Ser Gly Leu  
 1 5 10 15  
 Phe Gln Asp Gln Pro Leu Gly Ser Pro Pro Phe Leu Val Asn Cys Glu  
 20 25 30  
 Met Thr Ser Asp Gly Gly Trp Thr Val Asp Gln Arg Arg Leu Asn Gly  
 35 40 45  
 Ser Val Asp Phe Asn Gln Ser Trp Glu Ala Tyr Lys Asp Gly Phe Gly  
 50 55 60  
 Asp Pro Gln Gly Glu Phe Trp Leu Gly Leu Glu Lys Met His Ser Asp  
 65 70 75 80  
 Thr Gly Asn Arg Gly Ser Gln Leu Ala Val Gln Leu Gln Asp Trp Asp  
 85 90 95  
 Gly Asn Ala Lys Leu Leu Gln Phe Pro Asp His Leu Gly Gly Glu Asp  
 100 105 110  
 Thr Ala Tyr Ser Leu Gln Leu Thr Glu Pro Thr Ala Asn Glu Leu Gly  
 115 120 125  
 Ala Thr Asn Val Ser Pro Asn Gly Leu Ser Leu Pro Phe Ser Thr Trp  
 130 135 140  
 Asp Gln Asp His Asp Leu Arg Gly Asp Leu Asn Cys Ala Lys Ser Leu  
 145 150 155 160  
 Ser Gly Gly Trp Trp Phe Gly Thr Cys Ser His Ser Asn Leu Asn Gly  
 165 170 175  
 Gln Tyr Phe His Ser Asp Pro Arg Gln Arg Gln Glu Arg Lys Lys Gly  
 180 185 190  
 Asp Phe Trp Lys Thr Trp Lys Gly Arg Tyr Tyr Pro Leu Gln Ala Thr  
 195 200 205  
 Thr Leu Leu Asp Gln Pro  
 210

<210> 22  
 <211> 151  
 <212> PRT  
 <213> Homo sapiens

<400> 22

Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala Val Gln Arg Asp Ala Pro  
 1 5 10 15  
 Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu Gln Val Leu Glu Asn Asp  
 20 25 30  
 Met Glu Asn Asn Thr Gln Trp Leu Met Lys Leu Glu Asn Tyr Asp Gln  
 35 40 45  
 Asp Asn Met Lys Lys Glu Met Val Glu Asp Gln Gln Asn Ala Val Gln  
 50 55 60  
 Asn Gln Thr Ala Val Met Asp Glu Asp Gly Thr Asn Leu Leu Asn Gln  
 65 70 75 80  
 Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val Glu Ala Gln Val Leu  
 85 90 95  
 Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu Leu Glu His Ser Leu Ser  
 100 105 110  
 Thr Asn Lys Leu Glu Lys Gln Asp Leu Asp Gln Thr Ser Glu Asp Asn  
 115 120 125  
 Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu Lys Lys Val Leu Ala Met  
 130 135 140  
 Glu Asp Lys His Asp Asp Gln  
 145 150

<210> 23  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 23

Asn Tyr Asp Gln Asp Asn Met Lys Lys Glu Met Val Glu Asp Gln Gln  
 1 5 10 15  
 Asn Ala Val Gln Asn Gln Thr Ala Val Met Asp Glu Asp Gly Thr Asn  
 20 25 30  
 Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val Glu  
 35 40 45  
 Ala Gln  
 50

<210> 24  
 <211> 128  
 <212> PRT  
 <213> Homo sapiens

<400> 24

Cys Asp Leu Val Leu Ala Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met  
 1 5 10 15  
 Asp Ser Asp Gly Lys Lys Gln Tyr Gln Val Gln His Gly Ser Cys Ser  
 20 25 30  
 Tyr Thr Phe Leu Leu Pro Glu Met Asp Asn Cys Arg Ser Ser Ser  
 35 40 45  
 Pro Tyr Val Ser Asn Ala Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp  
 50 55 60  
 Asp Ser Val Gln Arg Leu Gln Val Leu Glu Asn Asp Met Glu Asn Asn  
 65 70 75 80  
 Thr Gln Trp Leu Met Lys Leu Glu Asn Tyr Asp Gln Asp Asn Met Lys  
 85 90 95  
 Lys Glu Met Val Glu Asp Gln Gln Asn Ala Val Gln Asn Gln Thr Ala  
 100 105 110  
 Val Met Asp Glu Asp Gly Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln  
 115 120 125

<210> 25  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 25

Pro Tyr Val Ser Asn Ala Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp  
 1 5 10 15  
 Asp Ser Val Gln Arg Leu Gln Val Leu Glu Asn Asp Met Glu Asn Asn  
 20 25 30  
 Thr Gln Trp Leu Met Lys Leu Glu Asn Tyr Asp Gln Asp Asn Met Lys  
 35 40 45  
 Lys Glu Met Val Glu Asp Gln Gln Asn Ala Val Gln Asn Gln Thr Ala  
 50 55 60  
 Val Met Asp Glu Asp Gly Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln  
 65 70 75 80  
 Thr Arg Lys Leu Thr Asp Val Glu Ala Gln Val Leu Asn Gln Thr Thr  
 85 90 95  
 Arg Leu Glu Leu Gln Leu Leu Glu His Ser Leu Ser Thr Asn Lys Leu  
 100 105 110  
 Glu Lys Gln Asp Leu Asp Gln Thr Ser Glu Asp Asn Lys Leu Gln Asp  
 115 120 125  
 Lys Asn Ser Phe Leu Glu Lys Lys Val Leu Ala Met Glu Asp Lys His  
 130 135 140



Asp Asp Gln Leu Gln Ser Asp Lys Glu Glu Lys Asp Gln Leu Gln Val  
 145 150 155 160  
 Leu Val Ser Lys Gln Asn Ser Asp Asp Glu Glu Leu Glu Lys Lys Asp  
 165 170 175  
 Val Thr Ala Thr Val Asn Asn Ser Val Leu Gln Lys Gln Gln His Asp  
 180 185 190  
 Leu Met Glu Thr  
 195

<210> 26  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<400> 26

Thr Asn Lys Leu Glu Arg Gln Met Leu Met Gln Ser Arg Glu Leu Gln  
 1 5 10 15  
 Arg Leu Gln Gly Arg Asn Arg Ala Leu Glu Thr Arg Leu Gln Ala Leu  
 20 25 30  
 Glu Ala Gln His Gln Ala Gln Leu Asn Ser Leu Gln Glu Lys Arg Glu  
 35 40 45  
 Gln Leu His Ser Leu Leu  
 50

<210> 27  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<400> 27

Ser Thr Asn Lys Leu Glu Asn Gln Leu Leu Leu Gln Arg Gln Lys Leu  
 1 5 10 15  
 Gln Gln Leu Gln Gly Gln Asn Ser Ala Leu Glu Lys Arg Leu Gln Ala  
 20 25 30  
 Leu Glu Thr Lys Gln Gln Glu Glu Leu Ala Ser Asp Leu Ser Lys Lys  
 35 40 45  
 Ala Lys Leu Leu Asn Thr Leu  
 50 55

<210> 28  
 <211> 101  
 <212> PRT  
 <213> Homo sapiens

<400> 28

Glu Leu Glu Leu Leu Asn Asn Glu Leu Leu Lys Gln Lys Arg Gln Asp  
 1 5 10 15  
 Glu Thr Leu Gln Gln Leu Val Glu Val Asp Gly Gly Asp Val Ser Glu  
 20 25 30  
 Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val Thr  
 35 40 45  
 Gln Leu Tyr Met Gln Leu Leu His Glu Asp Asp Arg Lys Arg Asp Asn  
 50 55 60  
 Ala Leu Glu Leu Ser Gln Leu Glu Asn Arg Asp Leu Asn Gln Thr Ala  
 65 70 75 80  
 Asp Met Leu Gln Leu Ala Ser Lys Tyr Lys Asp Leu Glu His Lys Tyr  
 85 90 95  
 Gln His Leu Ala Thr  
 100

<210> 29  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 29

Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg Val Asp Pro  
 1 5 10 15  
 Glu Val Ala Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln Asn Ser  
 20 25 30  
 Arg Asp Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg His Leu  
 35 40 45  
 Glu Lys Gln His Leu Arg Asp Gln His Leu Gln Ser Gln Phe Gly Leu  
 50 55 60  
 Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala Arg Arg  
 65 70 75 80  
 Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His Asn Val  
 85 90 95

&lt;210&gt; 30

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

Gln Leu Lys Ala Ala Asn Cys Cys Glu Glu Val Lys Glu Leu Lys Ala  
 1 5 10 15  
 Gln Val Ala Asn Leu Ser Ser Leu Leu Ser Glu Leu Asn Lys Lys Gln  
 20 25 30  
 Glu Arg Asp Trp Val Ser Val Val Met Gln Val Met Glu Leu Glu Ser  
 35 40 45  
 Asn Ser Lys Arg Met Glu Ser Arg Leu Thr Asp Ala Glu Ser Lys Tyr  
 50 55 60  
 Ser Glu Met Asn Asn Gln Asp Asp Asp Met Gln Leu Gln Ala Ala Gln  
 65 70 75 80

Thr Val Thr Gln

&lt;210&gt; 31

&lt;211&gt; 192

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

Gly Pro Asp Cys Val Asn Thr Lys Gly Gln Asp Ala Ser Thr Asp Lys  
 1 5 10 15  
 Asp Met Asp Thr Arg Met Asp Leu Glu Asn Leu Lys Asp Val Leu Ser  
 20 25 30  
 Arg Gln Lys Arg Glu Asp Asp Val Leu Gln Leu Val Val Asp Val Asp  
 35 40 45  
 Gly Asn Asp Val Asn Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn  
 50 55 60  
 Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu Asp  
 65 70 75 80  
 Asp Arg Lys Arg Asp Asn Ser Leu Glu Leu Ser Gln Leu Glu Asn Lys  
 85 90 95  
 Asp Leu Asn Val Thr Thr Glu Met Leu Lys Met Ala Thr Arg Tyr Arg  
 100 105 110  
 Glu Leu Glu Val Lys Tyr Ala Ser Leu Thr Asp Leu Val Asn Asn Gln  
 115 120 125  
 Ser Val Met Asp Thr Leu Leu Glu Glu Gln Cys Leu Arg Asp Phe Ser  
 130 135 140  
 Arg Gln Asp Thr His Val Ser Pro Pro Leu Val Gln Val Val Pro Gln  
 145 150 155 160  
 His Asp Pro Asn Ser Gln Gln Tyr Thr Pro Gly Leu Leu Gly Gly Asn  
 165 170 175

Glu Asp Gln Arg Asp Pro Gly Tyr Pro Arg Asp Leu Met Pro Pro Pro  
 180 185 190

<210> 32  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<400> 32

Ala Ala Asn Ala Ser Glu Leu Ala Ala Leu Arg Met Arg Val Gly Arg  
 1 5 10 15

His Glu Glu Leu Leu Arg Glu Leu Gln Arg Leu Ala Ala Ala Asp Gly  
 20 25 30

Ala Val Ala Gly Glu Val Arg Ala Leu Arg Lys Glu Ser Arg Gly Leu  
 35 40 45

Ser Ala Arg Leu Gly Gln Leu Arg Ala Gln Leu Gln His Glu Ala Gly  
 50 55 60

<210> 33  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<400> 33

Asp Leu Ser Leu Gln Thr Ser Glu Asp Lys Glu Glu Glu Lys Glu Leu  
 1 5 10 15

Arg Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu Val Lys Asn  
 20 25 30

Met Ser Leu Glu Leu Asn Ser Lys Leu Glu Ser Leu Leu Glu Glu Lys  
 35 40 45

Asp Leu Leu Gln Gln Lys Val Lys Tyr Leu Glu Glu Gln Leu Thr Asn  
 50 55 60

Leu Asp Gln Asn Gln Pro Glu  
 65 70

<210> 34  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 34

Leu Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg  
 1 5 10 15

Ser Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala  
 20 25

<210> 35  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens

<400> 35

Glu Thr Leu Gln Ser Leu Gln Thr Gln Leu Lys Ala Gln Asn Ser Lys  
 1 5 10 15

Asp Gln Gln Leu Phe Gln Lys Val Ala Gln Gln Gln Arg Tyr Leu Ser  
 20 25 30

Lys Gln Asn Leu Arg Asp Gln Asn Leu Gln Ser Gln Asp Asp Leu Leu  
 35 40 45

Ala

<210> 36  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 36

Val Ser Asn Ala Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser  
 1 5 10 15

Val Gln Arg Leu Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln  
 20 25 30  
 Trp Leu Met Lys Leu Glu Asn Ile Ser Gln Asp Asn Met Lys Lys Glu  
 35 40 45  
 Met Val Glu Ile Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met  
 50 55 60  
 Ile Glu Ile Gly Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg  
 65 70 75 80  
 Lys Leu Thr Asp Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu  
 85 90 95  
 Glu Leu Gln Leu Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys  
 100 105 110  
 Gln Ile Leu Asp Gln Thr Ser Glu  
 115 120

<210> 37  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 37

Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys  
 1 5 10 15  
 Leu Glu Asn Ile Ser Gln Asp Asn Met Lys Lys Glu Met Val Glu Ile  
 20 25 30  
 Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Ile Glu Ile Gly  
 35 40 45  
 Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp  
 50 55 60  
 Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu Leu Gln  
 65 70 75

<210> 38  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 38

Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp  
 1 5 10 15  
 Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu Leu Gln  
 20 25 30

<210> 39  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (78)..(78)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (103)..(120)  
 <223> "Xaa" may be any amino acid.

<400> 39

Thr Phe Pro Asn Ser Thr Glu Glu Ile Lys Leu Gln Ala Tyr Cys Asp  
 1 5 10 15  
 Met Glu Ala Gly Gly Gly Gly Trp Thr Ile Ile Gln Arg Arg Glu Asp  
 20 25 30  
 Gly Ser Val Ala Phe Gln Arg Thr Trp Lys Glu Tyr Lys Gln Gly Phe  
 35 40 45  
 Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln

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      50              55              60
Leu Thr Asn Gln Gln Arg Tyr Val Leu Lys Ile His Leu Xaa Asp Trp
65              70              75              80
Glu Gly Asn Glu Ala Tyr Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser
      85              90              95
Glu Glu Leu Asn Tyr Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      100              105              110
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      115              120

<210> 40
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(2)
<223> "Xaa" is Phe, Tyr, or His residue.

<220>
<221> misc_feature
<222> (6)..(6)
<223> "Xaa" is Asn or Leu residue.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" is Asp or Glu residue.

<220>
<221> misc_feature
<222> (8)..(8)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(9)
<223> "Xaa" is Ile, Leu, or Val residue.

<220>
<221> misc_feature
<222> (10)..(10)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (11)..(11)
<223> "Xaa" is Ile or Leu residue.

<220>
<221> misc_feature
<222> (12)..(26)
<223> "Xaa" may be any amino acid. There can be a deletion of up to two
      of the "Xaa" residues between positions 12 and 26.

<400> 40
Glu Xaa Trp Leu Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1              5              10              15
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Trp
      20              25

<210> 41
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (4)..(4)
<223> "Xaa" may be any amino acid.

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<220>
<221> misc_feature
<222> (6)..(6)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (8)..(8)
<223> "Xaa" is Asn or His.

<220>
<221> misc_feature
<222> (9)..(18)
<223> "Xaa" may be from 3 to 10 of any amino acid.

<220>
<221> misc_feature
<222> (20)..(20)
<223> "Xaa" is Ala or Ser.

<220>
<221> misc_feature
<222> (21)..(21)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (26)..(29)
<223> "Xaa" may be from 2 to 4 of any amino acid.

<400> 41
Phe Ser Thr Xaa Asp Xaa Asp Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1          5          10          15
Xaa Xaa Cys Xaa Xaa Gly Gly Trp Trp Xaa Xaa Xaa Xaa Cys
20          25          30

<210> 42
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(2)
<223> "Xaa" may be any amino acid.

<400> 42
Tyr Xaa Leu Arg Leu
1          5

<210> 43
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(2)
<223> "Xaa" may be any amino acid.

<400> 43
Tyr Xaa Leu Gln
1

<210> 44
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature

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<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 44
Phe Xaa Xaa His Xaa Gly Xaa Glu Xaa Xaa
1 5 10

<210> 45
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 45
Tyr Xaa Xaa His Xaa Gly Xaa Glu Xaa Xaa
1 5 10

<210> 46
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

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<400> 46

Phe Xaa Xaa Phe Xaa Gly Xaa Glu Xaa Xaa  
1 5 10

<210> 47

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (2)..(3)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (5)..(5)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (7)..(7)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (9)..(10)

<223> "Xaa" may be any amino acid.

<400> 47

Tyr Xaa Xaa Phe Xaa Gly Xaa Glu Xaa Xaa  
1 5 10

<210> 48

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (2)..(3)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (5)..(5)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (7)..(7)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (9)..(10)

<223> "Xaa" may be any amino acid.

<400> 48

Phe Xaa Xaa His Xaa Glu Xaa Glu Xaa Xaa  
1 5 10

<210> 49

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (2)..(3)

<223> "Xaa" may be any amino acid.



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<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 49
Phe Xaa Xaa Phe Xaa Glu Xaa Glu Xaa Xaa
1          5          10

<210> 50
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 50
Phe Xaa Xaa Phe Xaa Glu Xaa Glu Xaa Xaa
1          5          10

<210> 51
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 51
Tyr Xaa Xaa His Xaa Glu Xaa Glu Xaa Xaa

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1              5              10

<210> 52
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (2)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (5)..(5)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (7)..(7)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(10)
<223> "Xaa" may be any amino acid.

<400> 52
Tyr Xaa Xaa Phe Xaa Gly Xaa Glu Xaa Xaa
1              5              10

<210> 53
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 53
Xaa Xaa Xaa Thr Gly Xaa Xaa Xaa Ala Gly
1              5              10

<210> 54
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 54
Xaa Xaa Xaa Thr Gly Xaa Xaa Xaa Leu Gly
1              5              10

<210> 55

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<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 55
Xaa Xaa Xaa Thr Ala Xaa Xaa Xaa Ala Gly
1              5              10

<210> 56
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 56
Xaa Xaa Xaa Thr Ala Xaa Xaa Xaa Leu Gly
1              5              10

<210> 57
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 57
Xaa Xaa Xaa Val Gly Xaa Xaa Xaa Ala Gly
1              5              10

<210> 58
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

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<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 58

Xaa Xaa Xaa Val Gly Xaa Xaa Xaa Leu Gly  
 1 5 10

<210> 59  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 59

Xaa Xaa Xaa Val Ala Xaa Xaa Xaa Ala Gly  
 1 5 10

<210> 60  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 60

Xaa Xaa Xaa Val Ala Xaa Xaa Xaa Leu Gly  
 1 5 10

<210> 61  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 61

Xaa Xaa Xaa His Gly Xaa Xaa Xaa Ala Gly  
 1 5 10

<210> 62

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<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 62
Xaa Xaa Xaa His Gly Xaa Xaa Xaa Leu Gly
1          5          10

<210> 63
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 63
Xaa Xaa Xaa His Ala Xaa Xaa Xaa Ala Gly
1          5          10

<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(8)
<223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted
      between positions 6 and 8, inclusive.

<400> 64
Xaa Xaa Xaa His Ala Xaa Xaa Xaa Leu Gly
1          5          10

<210> 65
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(3)
<223> "Xaa" may be any amino acid.

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<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 65

Xaa Xaa Xaa Glu Gly Xaa Xaa Xaa Ala Gly  
 1 5 10

<210> 66  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 66

Xaa Xaa Xaa Glu Gly Xaa Xaa Xaa Leu Gly  
 1 5 10

<210> 67  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 67

Xaa Xaa Xaa Glu Ala Xaa Xaa Xaa Ala Gly  
 1 5 10

<210> 68  
 <211> 10  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (1)..(3)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(8)  
 <223> "Xaa" may be any amino acid. 1, 2, or 3 residues can be deleted  
 between positions 6 and 8, inclusive.

<400> 68

Xaa Xaa Xaa Glu Ala Xaa Xaa Xaa Leu Gly  
 1 5 10

<210> 69

<211> 34  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (4)..(4)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (6)..(6)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (10)..(10)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (12)..(12)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (16)..(20)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (30)..(30)  
 <223> "Xaa" may be any amino acid.

<400> 69

Phe Ser Thr Xaa Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Xaa  
 1 5 10 15

Xaa Xaa Xaa Xaa Gly Gly Trp Trp Phe Asp Ala Cys Gly Xaa Ser Asn  
 20 25 30

Leu Gly

<210> 70  
 <211> 29  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
 <221> misc\_feature  
 <222> (2)..(2)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (8)..(12)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (14)..(17)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (21)..(22)  
 <223> "Xaa" may be any amino acid.

<220>  
 <221> misc\_feature  
 <222> (25)..(25)  
 <223> "Xaa" may be any amino acid.

<400> 70

Glu Xaa Trp Leu Gly Asn Glu Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa  
1 5 10 15

Xaa Tyr Xaa Leu Xaa Xaa Glu Leu Xaa Asp Trp Glu Gly  
20 25

<210> 71

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (2)..(2)

<223> "Xaa" is His or Tyr residue.

<220>

<221> misc\_feature

<222> (8)..(8)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (9)..(9)

<223> "Xaa" is Asp or Val residue.

<220>

<221> misc\_feature

<222> (10)..(11)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (12)..(12)

<223> "Xaa" is Asp or Leu residue.

<220>

<221> misc\_feature

<222> (14)..(14)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature

<222> (15)..(15)

<223> "Xaa" is Arg or Gln residue.

<220>

<221> misc\_feature

<222> (16)..(17)

<223> "Xaa" may be any amino acid.

<400> 71

Glu Xaa Trp Leu Gly Asn Glu Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa  
1 5 10 15

Xaa

<210> 72

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc\_feature

<222> (4)..(4)

<223> "Xaa" is Leu or Lys residue.

<220>

<221> misc\_feature

<222> (6)..(6)

<223> "Xaa" may be any amino acid.

<220>

<221> misc\_feature



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<222> (10)..(10)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (12)..(12)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (16)..(16)
<223> "Xaa" is Ala or Ser residue.

<220>
<221> misc_feature
<222> (17)..(17)
<223> "Xaa" is Gln or Leu residue.

<220>
<221> misc_feature
<222> (18)..(18)
<223> "Xaa" is Met or Val residue.

<220>
<221> misc_feature
<222> (19)..(19)
<223> "Xaa" is Leu or Met residue.

<220>
<221> misc_feature
<222> (20)..(20)
<223> "Xaa" is Ser or Thr residue.

<220>
<221> misc_feature
<222> (30)..(30)
<223> "Xaa" is Leu or Pro.

<400> 72

Phe Ser Thr Xaa Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Xaa
1          5          10          15

Xaa Xaa Xaa Xaa Gly Gly Trp Trp Phe Asp Ala Cys Gly Xaa Ser Asn
          20          25          30

Leu Gly

<210> 73
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (3)..(3)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (6)..(6)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (9)..(9)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (12)..(12)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (14)..(16)
<223> "Xaa" may be any amino acid.

<220>
<221> misc_feature
<222> (20)..(20)

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<223> "Xaa" may be any amino acid.

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Cys Xaa Xaa Xaa Xaa Xaa Xaa  
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20 25 30
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Ser Gln Tyr Asp Xaa Phe Xaa Asp Gly Asn Glu Xaa Gln Xaa Tyr Arg
20      25      30
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20      25      30
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 20 25 30

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 35 40 45  
 Arg Glu Xaa Gly Xaa Xaa Xaa Phe Gln Arg Xaa Trp Xaa Xaa Tyr Lys  
 50 55 60  
 Xaa Gly Phe Gly Xaa Xaa Xaa Xaa Glu Xaa Trp Leu Gly Asn Glu Xaa  
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 Xaa Xaa Xaa Xaa Thr Xaa Xaa Xaa Xaa Tyr Xaa Leu Xaa Xaa Glu Leu  
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 Glu Xaa Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala  
 115 120 125  
 Gly Xaa Xaa Xaa Ser Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Ser Thr Xaa  
 130 135 140  
 Asp Xaa Asp Asn Asp Xaa Cys Xaa Cys Lys Cys Xaa Xaa Xaa Xaa  
 145 150 155 160  
 Gly Gly Trp Trp Phe Asp Ala Cys Gly Xaa Ser Asn Lys Asn Gly Xaa  
 165 170 175  
 Xaa Tyr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Lys Xaa Xaa Gly Asp Xaa Trp  
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<210> 87  
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<400> 87

Lys Met Gly Pro Lys Gly Glu Pro Gly Pro Arg Asn Cys Arg Glu Leu  
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 20 25 30  
 Glu Gly Arg Ala Leu Pro Val Phe Cys Asp Met Asp Thr Glu Gly Gly  
 35 40 45  
 Gly Trp Leu Val Phe Gln Arg Arg Gln Asp Gly Ser Val Asp Phe Phe  
 50 55 60  
 Arg Ser Trp Ser Ser Tyr Arg Ala Gly Phe Gly Asn Gln Glu Ser Glu  
 65 70 75 80  
 Phe Trp Leu Gly Asn Glu Asn Leu His Gln Leu Thr Leu Gln Gly Asn  
 85 90 95  
 Trp Glu Leu Arg Val Glu Leu Glu Asp Phe Asn Gly Asn Arg Thr Phe  
 100 105 110  
 Ala His Tyr Ala Thr Phe Arg Leu Leu Gly Glu Val Asp His Tyr Gln  
 115 120 125  
 Leu Ala Leu Gly Lys Phe Ser Glu Gly Thr Ala Gly Asp Ser Leu Ser  
 130 135 140  
 Leu His Ser Gly Arg Pro Phe Thr Thr Tyr Asp Ala Asp His Asp Ser  
 145 150 155 160

Ser Asn Ser Asn Cys Ala Val Ile Val His Gly Ala Trp Trp Tyr Ala  
 165 170 175  
 Ser Cys Tyr Arg Ser Asn Leu Asn Gly Arg Tyr Ala Val Ser Glu Ala  
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 Ala Ala His Lys Tyr Gly Ile Asp Trp Ala Ser Gly Arg Gly Val Gly  
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 His Pro Tyr Arg Arg Val Arg Met Met Leu Arg  
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<400> 88

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 Gly Pro Ala Cys Leu Lys Thr Gln Glu His Pro Ser Cys Pro Gly Pro  
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 Arg Glu Leu Glu Ala Ser Lys Val Val Leu Leu Pro Ser Cys Pro Gly  
 35 40 45  
 Ala Pro Gly Ser Pro Gly Glu Lys Gly Ala Pro Gly Pro Gln Gly Pro  
 50 55 60  
 Pro Gly Pro Pro Gly Lys Met Gly Pro Lys Gly Glu Pro Gly Asp Pro  
 65 70 75 80  
 Val Asn Leu Leu Arg Cys Gln Glu Gly Pro Arg Asn Cys Arg Glu Leu  
 85 90 95  
 Leu Ser Gln Gly Ala Thr Leu Ser Gly Trp Tyr His Leu Cys Leu Pro  
 100 105 110  
 Glu Gly Arg Ala Leu Pro Val Phe Cys Asp Met Asp Thr Glu Gly Gly  
 115 120 125  
 Gly Trp Leu Val Phe Gln Arg Gln Asp Gly Ser Val Asp Phe Phe  
 130 135 140  
 Arg Ser Trp Ser Ser Tyr Arg Ala Gly Phe Gly Asn Gln Glu Ser Glu  
 145 150 155 160  
 Phe Trp Leu Gly Asn Glu Asn Leu His Gln Leu Thr Leu Gln Gly Asn  
 165 170 175  
 Trp Glu Leu Arg Val Glu Leu Glu Asp Phe Asn Gly Asn Arg Thr Phe  
 180 185 190  
 Ala His Tyr Ala Thr Phe Arg Leu Leu Gly Glu Val Asp His Tyr Gln  
 195 200 205  
 Leu Ala Leu Gly Lys Phe Ser Glu Gly Thr Ala Gly Asp Ser Leu Ser  
 210 215 220  
 Leu His Ser Gly Arg Pro Phe Thr Thr Tyr Asp Ala Asp His Asp Ser  
 225 230 235 240  
 Ser Asn Ser Asn Cys Ala Val Ile Val His Gly Ala Trp Trp Tyr Ala  
 245 250 255  
 Ser Cys Tyr Arg Ser Asn Leu Asn Gly Arg Tyr Ala Val Ser Asp Ala  
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 Ala Ala His Lys Tyr Gly Ile Asp Trp Ala Ser Gly Arg Gly Val Gly  
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 His Pro Tyr Arg Arg Val Arg Met Met Leu Arg  
 290 295

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Xaa Xaa Xaa Trp Xaa Xaa Tyr Xaa Xaa Gly Phe Gly Xaa Xaa Xaa Xaa
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Xaa Xaa Trp Leu Gly Xaa Glu Xaa Xaa Xaa Xaa Leu Xaa
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Leu Gly Xaa Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Xaa Xaa His Xaa  
20 25 30

Xaa Xaa Xaa Phe Xaa Thr Xaa Asp Xaa Asp Xaa Xaa Xaa Xaa Cys  
35 40 45

Ala Xaa Xaa Xaa Xaa Gly Xaa Xaa Trp Tyr Xaa Xaa Cys Xaa Xaa Ser  
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Asn Leu Asn Gly

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Pro	Glu	Asn	Xaa	Asn	Xaa	Xaa	Xaa	Xaa	Met	Gln	Xaa	Xaa	Cys	Xaa	Xaa
		20						25					30		
Xaa	Xaa	Asp	Xaa	Gly	Gly	Trp	Xaa	Xaa	Xaa	Gln	Xaa	Arg	Xaa	Xaa	Gly
		35				40						45			
Xaa	Val	Asn	Phe	Xaa	Xaa	Asn	Trp	Glu	Xaa	Tyr	Xaa	Xaa	Gly	Phe	Gly
	50					55				60					
Asn	Asp	Asp	Xaa	Xaa	Xaa	Trp	Leu	Gly	Xaa	Glu	Asn	Asp	Tyr	Xaa	Leu
65					70					75					80
Xaa	Asn	Xaa	Xaa	Asn	Tyr	Lys	Leu	Xaa	Xaa	Xaa	Xaa	Glu	Asp	Xaa	Ser
				85				90						95	
Xaa	Xaa	Lys	Val	Xaa	Ala	Xaa	Tyr	Xaa	Ser	Phe	Arg	Leu	Glu	Pro	Glu
			100					105					110		
Ser	Glu	Xaa	Tyr	Xaa	Leu	Arg	Leu	Gly	Xaa	Tyr	Xaa	Tyr	Xaa	Xaa	Asn
		115					120					125			
Ala	Xaa	Xaa	Asp	Xaa	Xaa	Xaa	Trp	His	Xaa	Gly	Lys	Gln	Phe	Xaa	Thr
						135					140				
Leu	Asp	Arg	Asp	Xaa	Asp	Xaa	Tyr	Xaa	Gly	Xaa	Cys	Ala	His	Xaa	Xaa
145					150					155					160
Lys	Gly	Xaa	Xaa	Trp	Tyr	Xaa	Ala	Cys	Ala	His	Ser	Asn	Leu	Asn	Gly
				165				170						175	
Xaa	Xaa	Tyr	Arg	Gly	Gly	His	Tyr	Arg	Ser	Xaa	Xaa	Gln	Asp	Gly	Xaa
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Met Met Xaa  
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Arg Asp Cys Gln Glu Leu Phe Gln Xaa Gly Glu Arg Xaa Ser Gly Leu
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20          25          30
Met Thr Ser Asp Gly Gly Trp Thr Val Asp Gln Arg Arg Xaa Xaa Trp
35          40          45
Glu Ala Tyr Lys Xaa Gly Phe Gly Asp Pro Xaa Gly Glu Phe Trp Leu
50          55          60
Gly Leu Glu Lys Xaa His Ser Asp Xaa Gly Xaa Arg Xaa Ser Xaa Leu
65          70          75          80
Ala Val Gln Leu Xaa Asp Trp Asp Gly Asn Ala Xaa Leu Leu Gln Phe
85          90          95
Xaa Xaa His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu Thr
100         105         110
Xaa Pro Xaa Ala Xaa Xaa Leu Gly Ala Thr Thr Val Xaa Pro Xaa Gly
115         120         125
Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg Xaa
130         135         140
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Gln

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Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val  
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 Thr Gln Leu Tyr Met Gln Leu Leu His Glu Asp Asp Arg Lys Arg Asp  
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Asn

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Val Asp Gly Xaa Asp Val Xaa Glu Val Lys Leu Leu Arg Lys Glu Ser  
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 Arg Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His  
 20 25 30

Glu Asp Asp Arg Lys Arg Asp Asn Xaa Leu Glu Leu Ser Gln Leu Glu



35	40	45
Asn Xaa Asp Leu Asn		
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<400> 96
Leu Glu Xaa Leu Xaa Xaa Xaa Leu Xaa Xaa Gln Lys Arg Xaa Asp Xaa
1      5      10      15
Xaa Leu Gln Xaa Xaa Val Xaa Val Asp Gly Xaa Asp Val Xaa Glu Val
20      25      30
Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser Arg Val Thr Gln
35      40      45
Leu Tyr Met Gln Leu Leu His Glu Asp Asp Arg Lys Arg Asp Asn Xaa
50      55      60
Leu Glu Leu Ser Gln Leu Glu Asn Xaa Asp Leu Asn Xaa Thr Xaa Xaa
65      70      75      80
Met Leu Xaa Xaa Ala Xaa Xaa Tyr Xaa Xaa Leu Glu Xaa Lys Tyr Xaa
85      90      95

Xaa Leu

<210> 97
<211> 80
<212> PRT
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<223> "Xaa" may be any amino acid.

<400> 97

Tyr Xaa Xaa Asn Ala Xaa Gln Arg Asp Ala Pro Xaa Xaa Glu Xaa Asp
1      5      10      15
Xaa Ser Xaa Gln Xaa Leu Gln Xaa Leu Glu Xaa Xaa Met Glu Asn Xaa
20      25      30
Thr Gln Trp Leu Xaa Lys Leu Glu Asn Tyr Asp Xaa Xaa Asn Met Lys
35      40      45
Xaa Glu Met Xaa Xaa Asp Gln Gln Asn Ala Val Gln Asn Xaa Thr Ala
50      55      60
Xaa Met Xaa Glu Asp Gly Thr Xaa Leu Leu Xaa Gln Thr Ala Glu Gln
65      70      75      80

<210> 98
<211> 54
<212> PRT
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<220>
<223> Synthetic

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<220>  
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<400> 98

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Thr Asn Lys Leu Glu Xaa Gln Xaa Leu Xaa Gln Xaa Xaa Xaa Leu Gln
1          5          10          15

Xaa Leu Gln Gly Xaa Asn Xaa Ala Leu Glu Xaa Arg Leu Gln Ala Leu
20          25          30

Glu Xaa Xaa Xaa Gln Xaa Xaa Leu Xaa Ser Xaa Xaa Xaa Lys Xaa Xaa
35          40          45

Xaa Leu Xaa Xaa Xaa Leu
50

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<210> 99  
 <211> 33  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<220>  
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<220>  
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<220>  
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 <222> (27)..(27)  
 <223> "Xaa" may be any amino acid.

<400> 99

Thr Asn Lys Leu Glu Xaa Gln Xaa Leu Xaa Gln Xaa Xaa Xaa Leu Gln  
 1 5 10 15  
 Xaa Leu Gln Gly Xaa Asn Xaa Ala Leu Glu Xaa Arg Leu Gln Ala Leu  
 20 25 30

Glu

<210> 100  
 <211> 496  
 <212> PRT  
 <213> Homo sapiens

<400> 100

Met Trp Gln Asp Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala  
 1 5 10 15  
 Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Asp Gly Lys Lys  
 20 25 30  
 Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro  
 35 40 45  
 Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala  
 50 55 60  
 Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu  
 65 70 75 80  
 Gln Val Leu Glu Asn Asp Met Glu Asn Asn Thr Gln Trp Leu Met Lys  
 85 90 95

Leu Glu Asn Tyr Asp Gln Asp Asn Met Lys Lys Glu Met Val Glu Asp  
 100 105 110  
 Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Asp Glu Asp Gly  
 115 120 125  
 Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp  
 130 135 140  
 Val Glu Ala Gln Val Leu Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu  
 145 150 155 160  
 Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Asp Leu Asp  
 165 170 175  
 Gln Thr Ser Glu Asp Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu  
 180 185 190  
 Lys Lys Val Leu Ala Met Glu Asp Lys His Asp Asp Gln Leu Gln Ser  
 195 200 205  
 Asp Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn  
 210 215 220  
 Ser Asp Asp Glu Glu Leu Glu Lys Lys Asp Val Thr Ala Thr Val Asn  
 225 230 235 240  
 Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn  
 245 250 255  
 Asn Leu Leu Thr Met Met Ser Thr Ser Asn Ser Ala Lys Asp Pro Thr  
 260 265 270  
 Val Ala Lys Glu Glu Gln Asp Ser Phe Arg Asp Cys Ala Glu Val Phe  
 275 280 285  
 Lys Ser Gly His Thr Thr Asn Gly Asp Tyr Thr Leu Thr Phe Pro Asn  
 290 295 300  
 Ser Thr Glu Glu Asp Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly Gly  
 305 310 315 320  
 Gly Trp Thr Asp Asp Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln  
 325 330 335  
 Arg Thr Trp Lys Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu  
 340 345 350  
 Tyr Trp Leu Gly Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg  
 355 360 365  
 Tyr Val Leu Lys Asp His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr  
 370 375 380  
 Ser Leu Tyr Glu His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg  
 385 390 395 400  
 Asp His Leu Lys Gly Leu Thr Gly Thr Ala Gly Lys Asp Ser Ser Asp  
 405 410 415  
 Ser Gln Pro Gly Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys  
 420 425 430  
 Cys Asp Cys Lys Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp  
 435 440 445  
 Ala Cys Gly Pro Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln  
 450 455 460  
 Asn Thr Asn Lys Phe Asn Gly Asp Lys Trp Tyr Tyr Trp Lys Gly Ser  
 465 470 475 480  
 Gly Tyr Ser Leu Lys Ala Thr Thr Met Met Asp Arg Pro Ala Asp Phe  
 485 490 495  
  
 <210> 101  
 <211> 509  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 101  
 Met Leu Cys Gln Pro Ala Met Leu Leu Asp Gly Leu Leu Leu Leu Ala  
 1 5 10 15

Thr Met Ala Ala Ala Gln His Arg Gly Pro Glu Ala Gly Gly His Arg  
 20 25 30  
 Gln Asp His Gln Val Arg Arg Gly Gln Cys Ser Tyr Thr Phe Val Val  
 35 40 45  
 Pro Glu Pro Asp Asp Cys Gln Leu Ala Pro Thr Ala Ala Pro Glu Ala  
 50 55 60  
 Leu Gly Gly Ser Asn Ser Leu Gln Arg Asp Leu Pro Ala Ser Arg Leu  
 65 70 75 80  
 His Leu Thr Asp Trp Arg Ala Gln Arg Ala Gln Arg Ala Gln Arg Val  
 85 90 95  
 Ser Gln Leu Glu Lys Asp Leu Glu Asn Asn Thr Gln Trp Leu Leu Lys  
 100 105 110  
 Leu Glu Gln Ser Asp Lys Val Asn Leu Arg Ser His Leu Val Gln Ala  
 115 120 125  
 Gln Gln Asp Thr Asp Gln Asn Gln Thr Thr Thr Met Leu Ala Leu Gly  
 130 135 140  
 Ala Asn Leu Met Asn Gln Thr Lys Ala Gln Thr His Lys Leu Thr Ala  
 145 150 155 160  
 Val Glu Ala Gln Val Leu Asn Gln Thr Leu His Met Lys Thr Gln Met  
 165 170 175  
 Leu Glu Asn Ser Leu Ser Thr Asn Lys Leu Glu Arg Gln Met Leu Met  
 180 185 190  
 Gln Ser Arg Glu Leu Gln Arg Leu Gln Gly Arg Asn Arg Ala Leu Glu  
 195 200 205  
 Thr Arg Leu Gln Ala Leu Glu Ala Gln His Gln Ala Gln Leu Asn Ser  
 210 215 220  
 Leu Gln Glu Lys Arg Glu Gln Leu His Ser Leu Leu Gly His Gln Thr  
 225 230 235 240  
 Gly Thr Leu Ala Asn Leu Lys His Asn Leu His Ala Leu Ser Ser Asp  
 245 250 255  
 Ser Ser Ser Leu Gln Gln Gln Gln Gln Leu Thr Glu Phe Val Gln  
 260 265 270  
 Arg Leu Val Arg Asp Val Ala Gln Asp Gln His Pro Val Ser Leu Lys  
 275 280 285  
 Thr Pro Lys Pro Val Phe Gln Asp Cys Ala Glu Asp Lys Arg Ser Gly  
 290 295 300  
 Val Asn Thr Ser Gly Val Tyr Thr Asp Tyr Glu Thr Asn Met Thr Lys  
 305 310 315 320  
 Pro Leu Lys Val Phe Cys Asp Met Glu Thr Asp Gly Gly Gly Trp Thr  
 325 330 335  
 Leu Asp Gln His Arg Glu Asp Gly Ser Val Asn Phe Gln Arg Thr Trp  
 340 345 350  
 Glu Glu Tyr Lys Glu Gly Phe Gly Asn Val Ala Arg Glu His Trp Leu  
 355 360 365  
 Gly Asn Glu Ala Val His Arg Leu Thr Ser Arg Thr Ala Tyr Leu Leu  
 370 375 380  
 Arg Val Glu Leu His Asp Trp Glu Gly Arg Gln Thr Ser Asp Gln Tyr  
 385 390 395 400  
 Glu Asn Phe Gln Leu Gly Ser Glu Arg Gln Arg Tyr Ser Leu Ser Val  
 405 410 415  
 Asn Asp Ser Ser Ser Ala Gly Arg Lys Asn Ser Leu Ala Pro Gln  
 420 425 430  
 Gly Thr Lys Phe Ser Thr Lys Asp Met Asp Asn Asp Asn Cys Met Cys  
 435 440 445  
 Lys Cys Ala Gln Met Leu Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly  
 450 455 460

Leu Ser Asn Leu Asn Gly Asp Tyr Tyr Ser Val His Gln His Leu His  
465 470 475 480

Lys Asp Asn Gly Asp Arg Trp His Tyr Phe Arg Gly Pro Ser Tyr Ser  
485 490 495

Leu His Gly Thr Arg Met Met Leu Arg Pro Met Gly Ala  
500 505

<210> 102  
<211> 503  
<212> PRT  
<213> Homo sapiens

<400> 102

Met Leu Ser Gln Leu Ala Met Leu Gln Gly Ser Leu Leu Leu Val Val  
1 5 10 15

Ala Thr Met Ser Val Ala Gln Gln Thr Arg Gln Glu Ala Asp Arg Gly  
20 25 30

Cys Glu Thr Leu Val Val Gln His Gly His Cys Ser Tyr Thr Phe Leu  
35 40 45

Leu Pro Lys Ser Glu Pro Cys Pro Pro Gly Pro Glu Val Ser Arg Asp  
50 55 60

Ser Asn Thr Leu Gln Arg Glu Ser Leu Ala Asn Pro Leu His Leu Gly  
65 70 75 80

Lys Leu Pro Thr Gln Gln Val Lys Gln Leu Glu Gln Ala Leu Gln Asn  
85 90 95

Asn Thr Gln Trp Leu Lys Lys Leu Glu Arg Ala Asp Lys Thr Asp Leu  
100 105 110

Arg Ser Lys Leu Glu Gln Val Gln Gln Gln Met Ala Gln Asn Gln Thr  
115 120 125

Ala Pro Met Leu Glu Leu Gly Thr Ser Leu Leu Asn Gln Thr Thr Ala  
130 135 140

Gln Asp Arg Lys Leu Thr Asp Met Glu Ala Gln Leu Leu Asn Gln Thr  
145 150 155 160

Ser Arg Met Asp Ala Gln Met Pro Glu Thr Phe Leu Ser Thr Asn Lys  
165 170 175

Leu Glu Asn Gln Leu Leu Leu Gln Arg Gln Lys Leu Gln Gln Leu Gln  
180 185 190

Gly Gln Asn Ser Ala Leu Glu Lys Arg Leu Gln Ala Leu Glu Thr Lys  
195 200 205

Gln Gln Glu Glu Leu Ala Ser Asp Leu Ser Lys Lys Ala Lys Leu Leu  
210 215 220

Asn Thr Leu Ser Arg Gln Ser Ala Ala Leu Thr Asn Asp Glu Arg Gly  
225 230 235 240

Leu Arg Gly Val Arg His Asn Ser Ser Leu Leu Gln Asp Gln Gln His  
245 250 255

Ser Leu Arg Gln Leu Leu Val Leu Leu Arg His Leu Val Gln Glu Arg  
260 265 270

Ala Asn Ala Ser Ala Pro Ala Phe Asp Met Ala Gly Glu Gln Val Phe  
275 280 285

Gln Asp Cys Ala Glu Asp Gln Arg Ser Gly Ala Ser Ala Ser Gly Val  
290 295 300

Tyr Thr Asp Gln Val Ser Asn Ala Thr Lys Pro Arg Lys Val Phe Cys  
305 310 315 320

Asp Leu Gln Ser Ser Gly Gly Arg Trp Thr Leu Asp Gln Arg Arg Glu  
325 330 335

Asn Gly Thr Val Asn Phe Gln Arg Asn Trp Lys Asp Tyr Lys Gln Gly  
340 345 350

Phe Gly Asp Pro Ala Gly Glu His Trp Leu Gly Asn Glu Val Val His



355 360 365  
 Gln Leu Thr Arg Arg Ala Ala Tyr Ser Leu Arg Val Glu Leu Gln Asp  
 370 375 380  
 Trp Glu Gly His Glu Ala Tyr Ala Gln Tyr Glu His Phe His Leu Gly  
 385 390 395 400  
 Ser Glu Asn Gln Leu Tyr Arg Leu Ser Val Val Gly Tyr Ser Gly Ser  
 405 410 415  
 Ala Gly Arg Gln Ser Ser Leu Val Leu Gln Asn Thr Ser Phe Ser Thr  
 420 425 430  
 Leu Asp Ser Asp Asn Asp His Cys Leu Cys Lys Cys Ala Gln Val Met  
 435 440 445  
 Ser Gly Gly Trp Trp Phe Asp Ala Cys Gly Leu Ser Asn Leu Asn Gly  
 450 455 460  
 Val Tyr Tyr His Ala Pro Asp Asn Lys Tyr Lys Met Asp Gly Asp Arg  
 465 470 475 480  
 Trp His Tyr Phe Lys Gly Pro Ser Tyr Ser Leu Arg Ala Ser Arg Met  
 485 490 495  
 Met Asp Arg Pro Leu Asp Asp  
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 <210> 103  
 <211> 406  
 <212> PRT  
 <213> Homo sapiens  
 <400> 103  
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 Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser  
 50 55 60  
 Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys  
 65 70 75 80  
 Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg  
 85 90 95  
 Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln  
 100 105 110  
 Asn Ser Arg Asp Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg  
 115 120 125  
 His Leu Glu Lys Gln His Leu Arg Asp Gln His Leu Gln Ser Gln Phe  
 130 135 140  
 Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala  
 145 150 155 160  
 Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His  
 165 170 175  
 Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe  
 180 185 190  
 Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Asp Gln Pro Gln Gly  
 195 200 205  
 Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp  
 210 215 220  
 Thr Val Asp Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro  
 225 230 235 240  
 Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp  
 245 250 255

Leu Gly Leu Glu Lys Val His Ser Asp Thr Gly Asp Arg Asn Ser Arg  
 260 265 270  
 Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln  
 275 280 285  
 Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu  
 290 295 300  
 Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser  
 305 310 315 320  
 Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg  
 325 330 335  
 Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly  
 340 345 350  
 Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Asp Pro  
 355 360 365  
 Gln Gln Arg Gln Lys Leu Lys Lys Gly Asp Phe Trp Lys Thr Trp Arg  
 370 375 380  
 Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Asp Gln Pro Met  
 385 390 395 400  
 Ala Ala Glu Ala Ala Ser  
 405

<210> 104  
 <211> 459  
 <212> PRT  
 <213> Homo sapiens

<400> 104

Met Phe Thr Asp Lys Leu Leu Leu Phe Asp Val Pro Leu Val Asp Ser  
 1 5 10 15  
 Ser Arg Asp Asp Gln Asp Asn Ser Ser Phe Asp Ser Leu Ser Pro Glu  
 20 25 30  
 Pro Lys Ser Arg Phe Ala Met Leu Asp Asp Val Lys Asp Leu Ala Asn  
 35 40 45  
 Gly Leu Leu Gln Leu Gly His Gly Leu Lys Asp Phe Val His Lys Thr  
 50 55 60  
 Lys Gly Gln Asp Asn Asp Asp Phe Gln Lys Leu Asn Asp Phe Asp Gln  
 65 70 75 80  
 Ser Phe Tyr Asp Leu Ser Leu Gln Thr Ser Glu Asp Lys Glu Glu Glu  
 85 90 95  
 Lys Glu Leu Arg Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu  
 100 105 110  
 Val Lys Asn Met Ser Leu Glu Leu Asn Ser Lys Leu Glu Ser Leu Leu  
 115 120 125  
 Glu Glu Lys Asp Leu Leu Gln Gln Lys Val Lys Tyr Leu Glu Glu Gln  
 130 135 140  
 Leu Thr Asn Leu Asp Gln Asn Gln Pro Glu Thr Pro Glu His Pro Glu  
 145 150 155 160  
 Val Thr Ser Leu Lys Thr Phe Val Glu Lys Gln Asp Asn Ser Asp Lys  
 165 170 175  
 Asp Leu Leu Gln Thr Val Glu Asp Gln Tyr Lys Gln Leu Asn Gln Gln  
 180 185 190  
 His Ser Gln Asp Lys Glu Asp Glu Asn Gln Leu Arg Arg Thr Ser Asp  
 195 200 205  
 Gln Glu Pro Thr Glu Asp Ser Leu Ser Ser Lys Pro Arg Ala Pro Arg  
 210 215 220  
 Thr Thr Pro Phe Leu Gln Leu Asn Glu Asp Arg Asn Val Lys His Asp  
 225 230 235 240  
 Gly Asp Pro Ala Glu Cys Thr Thr Asp Tyr Asn Arg Gly Glu His Thr  
 245 250 255

Ser Gly Met Tyr Ala Asp Arg Pro Ser Asn Ser Gln Val Phe His Val  
 260 265 270  
 Tyr Cys Asp Val Asp Ser Gly Ser Pro Trp Thr Leu Asp Gln His Arg  
 275 280 285  
 Asp Asp Gly Ser Gln Asn Phe Asn Glu Thr Trp Glu Tyr Lys Tyr Gly  
 290 295 300  
 Phe Gly Arg Leu Asp Gly Glu Phe Trp Leu Gly Leu Glu Lys Asp Tyr  
 305 310 315 320  
 Ser Asp Val Lys Gln Ser Asn Tyr Val Leu Arg Asp Glu Leu Glu Asp  
 325 330 335  
 Trp Lys Asp Asn Lys His Tyr Asp Glu Tyr Ser Phe Tyr Leu Gly Asn  
 340 345 350  
 His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Asp Thr Gly Asn Val  
 355 360 365  
 Pro Asn Ala Asp Pro Glu Asn Lys Asp Leu Val Phe Ser Thr Trp Asp  
 370 375 380  
 His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr Ser Gly Gly  
 385 390 395 400  
 Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn Gly Lys Tyr  
 405 410 415  
 Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg Gly Leu Ser  
 420 425 430  
 Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Asp Lys Ser Thr Lys Met  
 435 440 445  
 Leu Asp His Pro Thr Asp Ser Glu Ser Phe Glu  
 450 455

<210> 105  
 <211> 493  
 <212> PRT  
 <213> Homo sapiens

<400> 105

Met Arg Pro Leu Cys Val Thr Cys Trp Trp Leu Gly Leu Leu Ala Ala  
 1 5 10 15  
 Met Gly Ala Val Ala Gly Gln Glu Asp Gly Phe Glu Gly Thr Glu Glu  
 20 25 30  
 Gly Ser Pro Arg Glu Phe Asp Tyr Leu Asn Arg Tyr Lys Arg Ala Gly  
 35 40 45  
 Glu Ser Gln Asp Lys Cys Thr Tyr Thr Phe Asp Val Pro Gln Gln Arg  
 50 55 60  
 Val Thr Gly Ala Asp Cys Val Asn Ser Lys Glu Pro Glu Val Leu Leu  
 65 70 75 80  
 Glu Asn Arg Val His Lys Gln Glu Leu Glu Leu Leu Asn Asn Glu Leu  
 85 90 95  
 Leu Lys Gln Lys Arg Gln Asp Glu Thr Leu Gln Gln Leu Val Glu Val  
 100 105 110  
 Asp Gly Gly Asp Val Ser Glu Val Lys Leu Leu Arg Lys Glu Ser Arg  
 115 120 125  
 Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu  
 130 135 140  
 Asp Asp Arg Lys Arg Asp Asn Ala Leu Glu Leu Ser Gln Leu Glu Asn  
 145 150 155 160  
 Arg Asp Leu Asn Gln Thr Ala Asp Met Leu Gln Leu Ala Ser Lys Tyr  
 165 170 175  
 Lys Asp Leu Glu His Lys Tyr Gln His Leu Ala Thr Leu Ala His Asn  
 180 185 190  
 Gln Ser Glu Asp Asp Ala Gln Leu Glu Glu His Cys Gln Arg Val Pro

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195          200          205
Ser Ala Arg Pro Val Pro Gln Pro Pro Pro Ala Ala Pro Pro Arg Val
210          215          220
Tyr Gln Pro Pro Thr Tyr Asn Arg Asp Asp Asn Gln Asp Ser Thr Asn
225          230          235
Glu Asp Gln Ser Asp Gln Asn Leu Lys Val Leu Pro Pro Pro Leu Pro
245          250          255
Thr Met Pro Thr Leu Thr Ser Leu Pro Ser Ser Thr Asp Lys Pro Ser
260          265          270
Gly Pro Trp Arg Asp Cys Leu Gln Ala Leu Glu Asp Gly His Asp Thr
275          280          285
Ser Ser Asp Tyr Leu Val Lys Pro Glu Asn Thr Asn Arg Leu Met Gln
290          295          300
Val Trp Cys Asp Gln Arg His Asp Pro Gly Gly Trp Thr Val Asp Gln
305          310          315
Arg Arg Leu Asp Gly Ser Val Asn Phe Phe Arg Asn Trp Glu Thr Tyr
325          330          335
Lys Gln Gly Phe Gly Asn Asp Asp Gly Glu Tyr Trp Leu Gly Leu Glu
340          345          350
Asn Asp Tyr Trp Leu Thr Asn Gln Gly Asn Tyr Lys Leu Leu Val Thr
355          360          365
Met Glu Asp Trp Ser Gly Arg Lys Val Phe Ala Glu Tyr Ala Ser Phe
370          375          380
Arg Leu Glu Pro Glu Ser Glu Tyr Tyr Lys Leu Arg Leu Gly Arg Tyr
385          390          395
His Gly Asn Ala Gly Asp Ser Phe Thr Trp His Asn Gly Lys Gln Phe
405          410          415
Thr Thr Leu Asp Arg Asp His Asp Val Tyr Thr Gly Asn Cys Ala His
420          425          430
Tyr Gln Lys Gly Gly Trp Trp Tyr Asn Ala Cys Ala His Ser Asn Leu
435          440          445
Asn Gly Val Trp Tyr Arg Gly Gly His Tyr Arg Ser Arg Tyr Gln Asp
450          455          460
Gly Val Tyr Trp Ala Glu Phe Arg Gly Gly Ser Tyr Ser Leu Lys Lys
465          470          475          480
Val Val Met Met Asp Arg Pro Asn Pro Asn Thr Phe His
485          490

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<210> 106
<211> 407
<212> PRT
<213> Homo sapiens

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<220>
<221> misc feature
<222> (222)..(222)
<223> "Xaa" may be any amino acid.

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<400> 106

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Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala
1          5          10          15
Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser
20          25          30
Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu
35          40          45
Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser
50          55          60
Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys
65          70          75          80
Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg

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				85				90				95			
Val	Asp	Pro	Glu 100	Val	Ala	Leu	His	Ser 105	Leu	Gln	Thr	Gln	Leu 110	Lys	Ala
Gln	Asn	Ser 115	Arg	Asp	Gln	Gln	Leu 120	Phe	His	Lys	Val	Ala 125	Gln	Gln	Gln
Arg	His 130	Leu	Glu	Lys	Gln	His 135	Leu	Arg	Asp	Gln	His 140	Leu	Gln	Ser	Gln
Phe 145	Gly	Leu	Leu	Asp	His 150	Lys	His	Leu	Asp	His 155	Glu	Val	Ala	Lys	Pro 160
Ala	Arg	Arg	Lys	Arg 165	Leu	Pro	Glu	Met	Ala 170	Gln	Pro	Val	Asp	Pro 175	Ala
His	Asn	Val	Ser 180	Arg	Leu	His	Arg	Leu 185	Pro	Arg	Asp	Cys	Gln 190	Glu	Leu
Phe	Gln	Val 195	Gly	Glu	Arg	Gln	Ser 200	Gly	Leu	Phe	Glu	Asp 205	Gln	Pro	Gln
Gly	Ser 210	Pro	Pro	Phe	Leu	Val 215	Asn	Cys	Lys	Met	Thr 220	Ser	Xaa	Gly	Gly
Trp 225	Thr	Val	Asp	Gln	Arg 230	Arg	His	Asp	Gly	Ser 235	Val	Asp	Phe	Asn	Arg 240
Pro	Trp	Glu	Ala	Tyr 245	Lys	Ala	Gly	Phe	Gly 250	Asp	Pro	His	Gly	Glu 255	Phe
Trp	Leu	Gly	Leu 260	Glu	Lys	Val	His	Ser 265	Asp	Thr	Gly	Asp	Arg 270	Asn	Ser
Arg	Leu	Ala 275	Val	Gln	Leu	Arg	Asp 280	Trp	Asp	Gly	Asn	Ala 285	Glu	Leu	Leu
Gln	Phe 290	Ser	Val	His	Leu	Gly 295	Gly	Glu	Asp	Thr	Ala 300	Tyr	Ser	Leu	Gln
Leu 305	Thr	Ala	Pro	Val	Ala 310	Gly	Gln	Leu	Gly	Ala 315	Thr	Thr	Val	Pro	Pro 320
Ser	Gly	Leu	Ser	Val 325	Pro	Phe	Ser	Thr	Trp 330	Asp	Gln	Asp	His	Asn 335	Leu
Arg	Arg	Asp	Lys 340	Asn	Cys	Ala	Lys	Ser 345	Leu	Ser	Gly	Gly	Trp 350	Trp	Phe
Gly	Thr	Cys 355	Ser	His	Ser	Asn	Leu 360	Asn	Gly	Gln	Tyr	Phe 365	Arg	Ser	Asp
Pro	Gln 370	Gln	Arg	Gln	Lys	Leu 375	Lys	Lys	Gly	Asp	Phe 380	Trp	Lys	Thr	Trp
Arg 385	Gly	Arg	Tyr	Tyr	Pro 390	Leu	Gln	Ala	Thr	Thr 395	Met	Leu	Asp	Gln	Pro 400
Met	Ala	Ala	Glu	Ala 405	Ala	Ser									

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<210> 107
<211> 288
<212> PRT
<213> Homo sapiens
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<400> 107

Met 1	Asp	Leu	Leu	Trp 5	Asp	Leu	Pro	Ser	Leu 10	Trp	Leu	Leu	Leu	Leu 15	Gly
Gly	Pro	Ala	Cys 20	Leu	Lys	Thr	Gln	Glu 25	His	Pro	Ser	Cys	Pro 30	Gly	Pro
Arg	Glu	Leu 35	Glu	Ala	Ser	Lys	Val 40	Val	Leu	Leu	Pro	Ser 45	Cys	Pro	Gly
Ala	Pro 50	Gly	Ser	Pro	Gly	Glu 55	Lys	Gly	Ala	Pro	Gly 60	Pro	Gln	Gly	Pro
Pro 65	Gly	Pro	Pro	Gly	Lys 70	Met	Gly	Pro	Lys 75	Gly	Glu	Pro	Gly	Pro	Arg 80

Asn Cys Arg Glu Leu Leu Ser Gln Gly Ala Thr Leu Ser Gly Trp Tyr  
 85 90 95  
 His Leu Cys Leu Pro Glu Gly Arg Ala Leu Pro Val Phe Cys Asp Met  
 100 105 110  
 Asp Thr Glu Gly Gly Gly Trp Leu Val Phe Gln Arg Arg Gln Asp Gly  
 115 120 125  
 Ser Val Asp Phe Phe Arg Ser Trp Ser Ser Tyr Arg Ala Gly Phe Gly  
 130 135 140  
 Asn Gln Glu Ser Glu Phe Trp Leu Gly Asn Glu Asn Leu His Gln Leu  
 145 150 155 160  
 Thr Leu Gln Gly Asn Trp Glu Leu Arg Val Glu Leu Glu Asp Phe Asn  
 165 170 175  
 Gly Asn Arg Thr Phe Ala His Tyr Ala Thr Phe Arg Leu Leu Gly Glu  
 180 185 190  
 Val Asp His Tyr Gln Leu Ala Leu Gly Lys Phe Ser Glu Gly Thr Ala  
 195 200 205  
 Gly Asp Ser Leu Ser Leu His Ser Gly Arg Pro Phe Thr Thr Tyr Asp  
 210 215 220  
 Ala Asp His Asp Ser Ser Asn Ser Asn Cys Ala Val Asp Val His Gly  
 225 230 235 240  
 Ala Trp Trp Tyr Ala Ser Cys Tyr Arg Ser Asn Leu Asn Gly Arg Tyr  
 245 250 255  
 Ala Val Ser Glu Ala Ala Ala His Lys Tyr Gly Asp Asp Trp Ala Ser  
 260 265 270  
 Gly Arg Gly Val Gly His Pro Tyr Arg Arg Val Arg Met Met Leu Arg  
 275 280 285

<210> 108  
 <211> 346  
 <212> PRT  
 <213> Homo sapiens  
 <400> 108

Met Leu Lys Lys Pro Leu Ser Ala Val Thr Trp Leu Cys Asp Phe Asp  
 1 5 10 15  
 Val Ala Phe Val Ser His Pro Ala Trp Leu Gln Lys Leu Ser Lys His  
 20 25 30  
 Lys Thr Pro Ala Gln Pro Gln Leu Lys Ala Ala Asn Cys Cys Glu Glu  
 35 40 45  
 Val Lys Glu Leu Lys Ala Gln Val Ala Asn Leu Ser Ser Leu Leu Ser  
 50 55 60  
 Glu Leu Asn Lys Lys Gln Glu Arg Asp Trp Val Ser Val Val Met Gln  
 65 70 75 80  
 Val Met Glu Leu Glu Ser Asn Ser Lys Arg Met Glu Ser Arg Leu Thr  
 85 90 95  
 Asp Ala Glu Ser Lys Tyr Ser Glu Met Asn Asn Gln Asp Asp Asp Met  
 100 105 110  
 Gln Leu Gln Ala Ala Gln Thr Val Thr Gln Thr Ser Ala Asp Ala Asp  
 115 120 125  
 Tyr Asp Cys Ser Ser Leu Tyr Gln Lys Asn Tyr Arg Asp Ser Gly Val  
 130 135 140  
 Tyr Lys Leu Pro Pro Asp Asp Phe Leu Gly Ser Pro Glu Leu Glu Val  
 145 150 155 160  
 Phe Cys Asp Met Glu Thr Ser Gly Gly Gly Trp Thr Asp Asp Gln Arg  
 165 170 175  
 Arg Lys Ser Gly Leu Val Ser Phe Tyr Arg Asp Trp Lys Gln Tyr Lys  
 180 185 190  
 Gln Gly Phe Gly Ser Asp Arg Gly Asp Phe Trp Leu Gly Asn Glu His  
 195 200 205

Asp His Arg Leu Ser Arg Gln Pro Thr Arg Leu Arg Val Glu Met Glu  
 210 215 220  
 Asp Trp Glu Gly Asn Leu Arg Tyr Ala Glu Tyr Ser His Phe Val Leu  
 225 230 235 240  
 Gly Asn Glu Leu Asn Ser Tyr Arg Leu Phe Leu Gly Asn Tyr Thr Gly  
 245 250 255  
 Asn Val Gly Asn Asp Ala Leu Gln Tyr His Asn Asn Thr Ala Phe Ser  
 260 265 270  
 Thr Lys Asp Lys Asp Asn Asp Asn Cys Leu Asp Lys Cys Ala Gln Leu  
 275 280 285  
 Arg Lys Gly Gly Tyr Trp Tyr Asn Cys Cys Thr Asp Ser Asn Leu Asn  
 290 295 300  
 Gly Val Tyr Tyr Arg Leu Gly Glu His Asn Lys His Leu Asp Gly Asp  
 305 310 315 320  
 Thr Trp Tyr Gly Trp His Gly Ser Thr Tyr Ser Leu Lys Arg Val Glu  
 325 330 335  
 Met Lys Asp Arg Pro Glu Asp Phe Lys Pro  
 340 345

<210> 109  
 <211> 346  
 <212> PRT  
 <213> Homo sapiens

<400> 109

Met Leu Lys Lys Pro Leu Ser Ala Val Thr Trp Leu Cys Ile Phe Ile  
 1 5 10 15  
 Val Ala Phe Val Ser His Pro Ala Trp Leu Gln Lys Leu Ser Lys His  
 20 25 30  
 Lys Thr Pro Ala Gln Pro Gln Leu Lys Ala Ala Asn Cys Cys Glu Glu  
 35 40 45  
 Val Lys Glu Leu Lys Ala Gln Val Ala Asn Leu Ser Ser Leu Leu Ser  
 50 55 60  
 Glu Leu Asn Lys Lys Gln Glu Arg Asp Trp Val Ser Val Val Met Gln  
 65 70 75 80  
 Val Met Glu Leu Glu Ser Asn Ser Lys Arg Met Glu Ser Arg Leu Thr  
 85 90 95  
 Asp Ala Glu Ser Lys Tyr Ser Glu Met Asn Asn Gln Ile Asp Ile Met  
 100 105 110  
 Gln Leu Gln Ala Ala Gln Thr Val Thr Gln Thr Ser Ala Asp Ala Ile  
 115 120 125  
 Tyr Asp Cys Ser Ser Leu Tyr Gln Lys Asn Tyr Arg Ile Ser Gly Val  
 130 135 140  
 Tyr Lys Leu Pro Pro Asp Phe Leu Gly Ser Pro Glu Leu Glu Val  
 145 150 155 160  
 Phe Cys Asp Met Glu Thr Ser Gly Gly Gly Trp Thr Ile Ile Gln Arg  
 165 170 175  
 Arg Lys Ser Gly Leu Val Ser Phe Tyr Arg Asp Trp Lys Gln Tyr Lys  
 180 185 190  
 Gln Gly Phe Gly Ser Ile Arg Gly Asp Phe Trp Leu Gly Asn Glu His  
 195 200 205  
 Ile His Arg Leu Ser Arg Gln Pro Thr Arg Leu Arg Val Glu Met Glu  
 210 215 220  
 Asp Trp Glu Gly Asn Leu Arg Tyr Ala Glu Tyr Ser His Phe Val Leu  
 225 230 235 240  
 Gly Asn Glu Leu Asn Ser Tyr Arg Leu Phe Leu Gly Asn Tyr Thr Gly  
 245 250 255  
 Asn Val Gly Asn Asp Ala Leu Gln Tyr His Asn Asn Thr Ala Phe Ser

260 265 270  
 Thr Lys Asp Lys Asp Asn Asp Asn Cys Leu Asp Lys Cys Ala Gln Leu  
 275 280 285  
 Arg Lys Gly Gly Tyr Trp Tyr Asn Cys Cys Thr Asp Ser Asn Leu Asn  
 290 295 300  
 Gly Val Tyr Tyr Arg Leu Gly Glu His Asn Lys His Leu Asp Gly Ile  
 305 310 315 320  
 Thr Trp Tyr Gly Trp His Gly Ser Thr Tyr Ser Leu Lys Arg Val Glu  
 325 330 335  
 Met Lys Ile Arg Pro Glu Asp Phe Lys Pro  
 340 345  
 <210> 110  
 <211> 491  
 <212> PRT  
 <213> Homo sapiens  
 <400> 110  
 Met Lys Thr Phe Thr Trp Thr Leu Gly Val Leu Phe Phe Leu Leu Val  
 1 5 10 15  
 Asp Thr Gly His Cys Arg Gly Gly Gln Phe Lys Asp Lys Lys Asp Asn  
 20 25 30  
 Gln Arg Arg Tyr Pro Arg Ala Thr Asp Gly Lys Glu Glu Ala Lys Lys  
 35 40 45  
 Cys Ala Tyr Thr Phe Leu Val Pro Glu Gln Arg Asp Thr Gly Pro Asp  
 50 55 60  
 Cys Val Asn Thr Lys Gly Gln Asp Ala Ser Thr Asp Lys Asp Met Asp  
 65 70 75 80  
 Thr Arg Met Asp Leu Glu Asn Leu Lys Asp Val Leu Ser Arg Gln Lys  
 85 90 95  
 Arg Glu Asp Asp Val Leu Gln Leu Val Val Asp Val Asp Gly Asn Asp  
 100 105 110  
 Val Asn Glu Val Lys Leu Leu Arg Lys Glu Ser Arg Asn Met Asn Ser  
 115 120 125  
 Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu Asp Asp Arg Lys  
 130 135 140  
 Arg Asp Asn Ser Leu Glu Leu Ser Gln Leu Glu Asn Lys Asp Leu Asn  
 145 150 155 160  
 Val Thr Thr Glu Met Leu Lys Met Ala Thr Arg Tyr Arg Glu Leu Glu  
 165 170 175  
 Val Lys Tyr Ala Ser Leu Thr Asp Leu Val Asn Asn Gln Ser Val Met  
 180 185 190  
 Asp Thr Leu Leu Glu Glu Gln Cys Leu Arg Asp Phe Ser Arg Gln Asp  
 195 200 205  
 Thr His Val Ser Pro Pro Leu Val Gln Val Val Pro Gln His Asp Pro  
 210 215 220  
 Asn Ser Gln Gln Tyr Thr Pro Gly Leu Leu Gly Gly Asn Glu Asp Gln  
 225 230 235 240  
 Arg Asp Pro Gly Tyr Pro Arg Asp Leu Met Pro Pro Pro Asp Leu Ala  
 245 250 255  
 Thr Ser Pro Thr Lys Ser Pro Phe Lys Asp Pro Pro Val Thr Phe Asp  
 260 265 270  
 Asn Glu Gly Pro Phe Lys Asp Cys Gln Gln Ala Lys Glu Ala Gly His  
 275 280 285  
 Ser Val Ser Gly Asp Tyr Met Asp Lys Pro Glu Asn Ser Asn Gly Pro  
 290 295 300  
 Met Gln Leu Trp Cys Glu Asn Ser Leu Asp Pro Gly Gly Trp Thr Val  
 305 310 315 320



Asp Gln Lys Arg Thr Asp Gly Ser Val Asn Phe Phe Arg Asn Trp Glu  
 325 335  
 Asn Tyr Lys Lys Gly Phe Gly Asn Asp Asp Gly Glu Tyr Trp Leu Gly  
 340 345 350  
 Leu Glu Asn Asp Tyr Met Leu Ser Asn Gln Asp Asn Tyr Lys Leu Leu  
 355 360 365  
 Asp Glu Leu Glu Asp Trp Ser Asp Lys Lys Val Tyr Ala Glu Tyr Ser  
 370 375 380  
 Ser Phe Arg Leu Glu Pro Glu Ser Glu Phe Tyr Arg Leu Arg Leu Gly  
 385 390 395 400  
 Thr Tyr Gln Gly Asn Ala Gly Asp Ser Met Met Trp His Asn Gly Lys  
 405 410 415  
 Gln Phe Thr Thr Leu Asp Arg Asp Lys Asp Met Tyr Ala Gly Asn Cys  
 420 425 430  
 Ala His Phe His Lys Gly Gly Trp Trp Tyr Asn Ala Cys Ala His Ser  
 435 440 445  
 Asn Leu Asn Gly Val Trp Tyr Arg Gly Gly His Tyr Arg Ser Lys His  
 450 455 460  
 Gln Asp Gly Asp Phe Trp Ala Glu Tyr Arg Gly Gly Ser Tyr Ser Leu  
 465 470 475 480  
 Arg Ala Val Gln Met Met Asp Lys Pro Asp Asp  
 485 490

<210> 111  
 <211> 460  
 <212> PRT  
 <213> Homo sapiens

<400> 111

Met Phe Thr Asp Lys Leu Leu Leu Phe Asp Val Pro Leu Val Asp Ser  
 1 5 10 15  
 Ser Arg Asp Asp Gln Asp Asn Ser Ser Phe Asp Ser Leu Ser Pro Glu  
 20 25 30  
 Pro Lys Ser Arg Phe Ala Met Leu Asp Asp Val Lys Asp Leu Ala Asn  
 35 40 45  
 Gly Leu Leu Gln Leu Gly His Gly Leu Lys Asp Phe Val His Lys Thr  
 50 55 60  
 Lys Gly Gln Asp Asn Asp Asp Phe Gln Lys Leu Asn Asp Phe Asp Gln  
 65 70 75 80  
 Ser Phe Tyr Asp Leu Ser Leu Gln Thr Ser Glu Asp Lys Glu Glu Glu  
 85 90 95  
 Lys Glu Leu Arg Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu  
 100 105 110  
 Val Lys Asn Met Ser Leu Glu Leu Asn Ser Lys Leu Glu Ser Leu Leu  
 115 120 125  
 Glu Glu Lys Asp Leu Leu Gln Gln Lys Val Lys Tyr Leu Glu Glu Gln  
 130 135 140  
 Leu Thr Asn Leu Asp Gln Asn Gln Pro Glu Thr Pro Glu His Pro Glu  
 145 150 155 160  
 Val Thr Ser Leu Lys Thr Phe Val Glu Lys Gln Asp Asn Ser Asp Lys  
 165 170 175  
 Asp Leu Leu Gln Thr Val Glu Asp Gln Tyr Lys Gln Leu Asn Gln Gln  
 180 185 190  
 His Ser Gln Asp Lys Glu Asp Glu Asn Gln Leu Arg Arg Thr Ser Asp  
 195 200 205  
 Gln Glu Pro Thr Glu Asp Ser Leu Ser Ser Lys Pro Arg Ala Pro Arg  
 210 215 220  
 Thr Thr Pro Phe Leu Gln Leu Asn Glu Asp Arg Asn Val Lys His Asp  
 225 230 235 240

Gly Asp Pro Ala Glu Cys Thr Thr Asp Tyr Asn Arg Gly Glu His Thr  
 245 250 255  
 Ser Gly Met Tyr Ala Asp Arg Pro Ser Asn Ser Gln Val Phe His Val  
 260 265 270  
 Tyr Cys Asp Val Asp Ser Gly Ser Pro Trp Thr Leu Asp Gln His Arg  
 275 280 285  
 Asp Asp Gly Ser Gln Asn Phe Asn Glu Thr Trp Glu Asn Tyr Lys Tyr  
 290 295 300  
 Gly Phe Gly Arg Leu Asp Gly Glu Phe Trp Leu Gly Leu Glu Lys Asp  
 305 310 315  
 Tyr Ser Asp Val Lys Gln Ser Asn Tyr Val Leu Arg Asp Glu Leu Glu  
 325 330 335  
 Asp Trp Lys Asp Asn Lys His Tyr Asp Glu Tyr Ser Phe Tyr Leu Gly  
 340 345 350  
 Asn His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Asp Thr Gly Asn  
 355 360 365  
 Val Pro Asn Ala Asp Pro Glu Asn Lys Asp Leu Val Phe Ser Thr Trp  
 370 375 380  
 Asp His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr Ser Gly  
 385 390 395 400  
 Gly Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn Gly Lys  
 405 410 415  
 Tyr Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg Gly Leu  
 420 425 430  
 Ser Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Asp Lys Ser Thr Lys  
 435 440 445  
 Met Leu Asp His Pro Thr Asp Ser Glu Ser Phe Glu  
 450 455 460

<210> 112  
 <211> 470  
 <212> PRT  
 <213> Homo sapiens

<400> 112

Met Gly Lys Pro Trp Leu Arg Ala Leu Gln Leu Leu Leu Leu Gly  
 1 5 10 15  
 Ala Ser Trp Ala Arg Ala Gly Ala Pro Arg Cys Thr Tyr Thr Phe Val  
 20 25 30  
 Leu Pro Pro Gln Lys Phe Thr Gly Ala Val Cys Trp Ser Gly Pro Ala  
 35 40 45  
 Ser Thr Arg Ala Thr Pro Glu Ala Ala Asn Ala Ser Glu Leu Ala Ala  
 50 55 60  
 Leu Arg Met Arg Val Gly Arg His Glu Glu Leu Leu Arg Glu Leu Gln  
 65 70 75 80  
 Arg Leu Ala Ala Ala Asp Gly Ala Val Ala Gly Glu Val Arg Ala Leu  
 85 90 95  
 Arg Lys Glu Ser Arg Gly Leu Ser Ala Arg Leu Gly Gln Leu Arg Ala  
 100 105 110  
 Gln Leu Gln His Glu Ala Gly Pro Gly Ala Gly Pro Gly Ala Asp Leu  
 115 120 125  
 Gly Ala Glu Pro Ala Ala Ala Leu Ala Leu Leu Gly Glu Arg Val Leu  
 130 135 140  
 Asn Ala Ser Ala Glu Ala Gln Arg Ala Ala Ala Arg Phe His Gln Leu  
 145 150 155 160  
 Asp Val Lys Phe Arg Glu Leu Ala Gln Leu Val Thr Gln Gln Ser Ser  
 165 170 175  
 Leu Asp Ala Arg Leu Glu Arg Leu Cys Pro Gly Gly Ala Gly Gly Gln

180 185 190  
 Gln Gln Val Leu Pro Pro Pro Pro Leu Val Pro Val Val Pro Val Arg  
 195 200 205  
 Leu Val Gly Ser Thr Ser Asp Thr Ser Arg Met Leu Asp Pro Ala Pro  
 210 215 220  
 Glu Pro Gln Arg Asp Gln Thr Gln Arg Gln Gln Glu Pro Met Ala Ser  
 225 230 235 240  
 Pro Met Pro Ala Gly His Pro Ala Val Pro Thr Lys Pro Val Gly Pro  
 245 250 255  
 Trp Gln Asp Cys Ala Glu Ala Arg Gln Ala Gly His Glu Gln Ser Gly  
 260 265 270  
 Val Tyr Glu Leu Arg Val Gly Arg His Val Val Ser Val Trp Cys Glu  
 275 280 285  
 Gln Gln Leu Glu Gly Gly Gly Trp Thr Val Asp Gln Arg Arg Gln Asp  
 290 295 300  
 Gly Ser Val Asn Phe Phe Thr Thr Trp Gln His Tyr Lys Ala Gly Phe  
 305 310 315 320  
 Gly Arg Pro Asp Gly Glu Tyr Trp Leu Gly Leu Glu Pro Val Tyr Gln  
 325 330 335  
 Leu Thr Ser Arg Gly Asp His Glu Leu Leu Val Leu Leu Glu Asp Trp  
 340 345 350  
 Gly Gly Arg Gly Ala Arg Ala His Tyr Asp Gly Phe Ser Leu Glu Pro  
 355 360 365  
 Glu Ser Asp His Tyr Arg Leu Arg Leu Gly Gln Tyr His Gly Asp Ala  
 370 375 380  
 Gly Asp Ser Leu Ser Trp His Asn Asp Lys Pro Phe Ser Thr Val Asp  
 385 390 395 400  
 Arg Asp Arg Asp Ser Tyr Ser Gly Asn Cys Ala Leu Tyr Gln Arg Gly  
 405 410 415  
 Gly Trp Trp Tyr His Ala Cys Ala His Ser Asn Leu Asn Gly Val Trp  
 420 425 430  
 His His Gly Gly His Tyr Arg Ser Arg Tyr Gln Asp Gly Val Tyr Trp  
 435 440 445  
 Ala Glu Phe Arg Gly Gly Ala Tyr Ser Leu Arg Lys Ala Ala Met Leu  
 450 455 460  
 Asp Arg Pro Leu Lys Leu  
 465 470  
 <210> 113  
 <211> 214  
 <212> PRT  
 <213> Homo sapiens  
 <400> 113

Met Leu Cys Ala Ala Thr Ala Val Leu Leu Thr Ala Gln Gly Gly Pro  
 1 5 10 15  
 Val Gln Ser Lys Ser Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val  
 20 25 30  
 Leu Ala His Gly Leu Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala  
 35 40 45  
 Glu Arg Thr Arg Ser Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala  
 50 55 60  
 Cys Gly Ser Ala Cys Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu  
 65 70 75 80  
 Ala Pro Glu Thr Arg Val Asp Pro Glu Val Leu His Thr Leu Gln Thr  
 85 90 95  
 Gln Leu Lys Ala Gln Asn Thr Arg Ile Gln Gln Leu Phe His Lys Val  
 100 105 110

Ala Gln Gln Gln Arg His Leu Glu Lys Gln His Leu Arg Ile Gln His  
 115 120 125  
 Leu Gln Ser Gln Phe Gly Leu Leu Asp His Lys His Leu Asp His Glu  
 130 135 140  
 Val Ala Lys Pro Ala Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro  
 145 150 155 160  
 Val Asp Pro Ala His Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp  
 165 170 175  
 Cys Gln Glu Leu Phe Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu  
 180 185 190  
 Ile Gln Pro Gln Gly Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr  
 195 200 205  
 Ser Asp Gly Gly Trp Thr  
 210

<210> 114  
 <211> 405  
 <212> PRT  
 <213> Homo sapiens

<400> 114

Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala  
 1 5 10 15  
 Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly Gln Gly Cys Ala Asn Thr Gly Ala His Pro Gln Ser  
 50 55 60  
 Ala Glu Arg Ala Gly Ala Arg Leu Ser Ala Cys Gly Ser Ala Cys Gln  
 65 70 75 80  
 Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg Val  
 85 90 95  
 Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln Asn  
 100 105 110  
 Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg His  
 115 120 125  
 Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe Gly  
 130 135 140  
 Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala Arg  
 145 150 155 160  
 Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His Asn  
 165 170 175  
 Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe Gln  
 180 185 190  
 Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly Ser  
 195 200 205  
 Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp Thr  
 210 215 220  
 Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro Trp  
 225 230 235 240  
 Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp Leu  
 245 250 255  
 Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg Leu  
 260 265 270  
 Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln Phe  
 275 280 285  
 Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu Thr  
 290 295 300

Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser Gly  
 305 310 315 320  
 Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg Arg  
 325 330 335  
 Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly Thr  
 340 345 350  
 Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro Gln  
 355 360 365  
 Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg Gly  
 370 375 380  
 Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met Ala  
 385 390 395 400  
 Ala Glu Ala Ala Ser  
 405

<210> 115  
 <211> 410  
 <212> PRT  
 <213> Homo sapiens

<400> 115

Met Arg Cys Ala Pro Thr Ala Gly Ala Ala Leu Val Leu Cys Ala Ala  
 1 5 10 15  
 Thr Ala Gly Leu Leu Ser Ala Gln Gly Arg Pro Ala Gln Pro Glu Pro  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Leu Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly His Gly Leu Arg Glu His Val Glu Arg Thr Arg Gly  
 50 55 60  
 Gln Leu Gly Ala Leu Glu Arg Arg Met Ala Ala Cys Gly Asn Ala Cys  
 65 70 75 80  
 Gln Gly Pro Lys Gly Lys Asp Ala Pro Phe Lys Asp Ser Glu Asp Arg  
 85 90 95  
 Val Pro Glu Gly Gln Thr Pro Glu Thr Leu Gln Ser Leu Gln Thr Gln  
 100 105 110  
 Leu Lys Ala Gln Asn Ser Lys Ile Gln Gln Leu Phe Gln Lys Val Ala  
 115 120 125  
 Gln Gln Gln Arg Tyr Leu Ser Lys Gln Asn Leu Arg Ile Gln Asn Leu  
 130 135 140  
 Gln Ser Gln Ile Asp Leu Leu Ala Pro Thr His Leu Asp Asn Gly Val  
 145 150 155 160  
 Asp Lys Thr Ser Arg Gly Lys Arg Leu Pro Lys Met Thr Gln Leu Ile  
 165 170 175  
 Gly Leu Thr Pro Asn Ala Thr His Leu His Arg Pro Pro Arg Asp Cys  
 180 185 190  
 Gln Glu Leu Phe Gln Glu Gly Glu Arg His Ser Gly Leu Phe Gln Ile  
 195 200 205  
 Gln Pro Leu Gly Ser Pro Pro Phe Leu Val Asn Cys Glu Met Thr Ser  
 210 215 220  
 Asp Gly Gly Trp Thr Val Ile Gln Arg Arg Leu Asn Gly Ser Val Asp  
 225 230 235 240  
 Phe Asn Gln Ser Trp Glu Ala Tyr Lys Asp Gly Phe Gly Asp Pro Gln  
 245 250 255  
 Gly Glu Phe Trp Leu Gly Leu Glu Lys Met His Ser Ile Thr Gly Asn  
 260 265 270  
 Arg Gly Ser Gln Leu Ala Val Gln Leu Gln Asp Trp Asp Gly Asn Ala  
 275 280 285  
 Lys Leu Leu Gln Phe Pro Ile His Leu Gly Gly Glu Asp Thr Ala Tyr

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      290              295              300
Ser Leu Gln Leu Thr Glu Pro Thr Ala Asn Glu Leu Gly Ala Thr Asn
305      310      315      320
Val Ser Pro Asn Gly Leu Ser Leu Pro Phe Ser Thr Trp Asp Gln Asp
      325      330      335
His Asp Leu Arg Gly Asp Leu Asn Cys Ala Lys Ser Leu Ser Gly Gly
      340      345      350
Trp Trp Phe Gly Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe
      355      360      365
His Ser Ile Pro Arg Gln Arg Gln Glu Arg Lys Lys Gly Ile Phe Trp
      370      375      380
Lys Thr Trp Lys Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Leu Leu
385      390      395      400
Ile Gln Pro Met Glu Ala Thr Ala Ala Ser
      405      410

<210> 116
<211> 470
<212> PRT
<213> Homo sapiens

<400> 116
Met Gly Lys Pro Trp Leu Arg Ala Leu Gln Leu Leu Leu Leu Gly
1      5      10      15
Ala Ser Trp Ala Arg Ala Gly Ala Pro Arg Cys Thr Tyr Thr Phe Val
      20      25      30
Leu Pro Pro Gln Lys Phe Thr Gly Ala Val Cys Trp Ser Gly Pro Ala
      35      40      45
Ser Thr Arg Ala Thr Pro Glu Ala Ala Asn Ala Ser Glu Leu Ala Ala
      50      55      60
Leu Arg Met Arg Val Gly Arg His Glu Glu Leu Leu Arg Glu Leu Gln
      65      70      75      80
Arg Leu Ala Ala Ala Asp Gly Ala Val Ala Gly Lys Val Arg Ala Leu
      85      90      95
Arg Lys Glu Ser Arg Gly Leu Ser Ala Arg Leu Gly Gln Leu Arg Ala
      100      105      110
Gln Leu Gln His Glu Ala Gly Pro Gly Ala Gly Pro Gly Ala Asp Leu
      115      120      125
Gly Ala Glu Pro Ala Ala Ala Leu Ala Leu Leu Gly Glu Arg Val Leu
      130      135      140
Asn Ala Ser Ala Glu Ala Gln Arg Ala Ala Ala Arg Phe His Gln Leu
      145      150      155      160
Asp Val Lys Phe Arg Glu Leu Ala Gln Leu Val Thr Gln Gln Ser Ser
      165      170      175
Leu Ile Ala Arg Leu Glu Arg Leu Cys Pro Gly Gly Ala Gly Gly Gln
      180      185      190
Gln Gln Val Leu Pro Pro Pro Pro Leu Val Pro Val Val Pro Val Arg
      195      200      205
Leu Val Gly Ser Thr Ser Asp Thr Ser Arg Met Leu Asp Pro Ala Pro
      210      215      220
Glu Pro Gln Arg Asp Gln Thr Gln Arg Gln Gln Glu Pro Met Ala Ser
      225      230      235      240
Pro Met Pro Ala Gly His Pro Ala Val Pro Thr Lys Pro Val Gly Pro
      245      250      255
Trp Gln Asp Cys Ala Glu Ala Arg Gln Ala Gly His Glu Gln Ser Gly
      260      265      270
Val Tyr Glu Leu Arg Val Gly Arg His Val Val Ser Val Trp Cys Glu
      275      280      285

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Gln Gln Leu Glu Gly Gly Gly Trp Thr Val Ile Gln Arg Arg Gln Asp  
 290 295 300  
 Gly Ser Val Asn Phe Phe Thr Thr Trp Gln His Tyr Lys Ala Gly Phe  
 305 310 320  
 Gly Arg Pro Asp Gly Glu Tyr Trp Leu Gly Leu Glu Pro Val Tyr Gln  
 325 330 335  
 Leu Thr Ser Arg Gly Asp His Glu Leu Leu Val Leu Leu Glu Asp Trp  
 340 345 350  
 Gly Gly Arg Gly Ala Arg Ala His Tyr Asp Gly Phe Ser Leu Glu Pro  
 355 360 365  
 Glu Ser Asp His Tyr Arg Leu Arg Leu Gly Gln Tyr His Gly Asp Ala  
 370 375 380  
 Gly Asp Ser Leu Ser Trp His Asn Asp Lys Pro Phe Ser Thr Val Asp  
 385 390 395 400  
 Arg Asp Arg Asp Ser Tyr Ser Gly Asn Cys Ala Leu Tyr Gln Arg Gly  
 405 410 415  
 Gly Trp Trp Tyr His Ala Cys Ala His Ser Asn Leu Asn Gly Val Trp  
 420 425 430  
 His His Gly Gly His Tyr Arg Ser Arg Tyr Gln Asp Gly Val Tyr Trp  
 435 440 445  
 Ala Glu Phe Arg Gly Gly Ala Tyr Ser Leu Arg Lys Ala Ala Met Leu  
 450 455 460  
 Ile Arg Pro Leu Lys Leu  
 465 470

<210> 117  
 <211> 410  
 <212> PRT  
 <213> Homo sapiens

<400> 117

Met Arg Cys Ala Pro Thr Ala Gly Ala Ala Leu Val Leu Cys Ala Ala  
 1 5 10 15  
 Thr Ala Gly Leu Leu Ser Ala Gln Gly Arg Pro Ala Gln Pro Glu Pro  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Leu Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly His Gly Leu Arg Glu His Val Glu Arg Thr Arg Gly  
 50 55 60  
 Gln Leu Gly Ala Leu Glu Arg Arg Met Ala Ala Cys Gly Asn Ala Cys  
 65 70 75 80  
 Gln Gly Pro Lys Gly Lys Asp Ala Pro Phe Lys Asp Ser Glu Asp Arg  
 85 90 95  
 Val Pro Glu Gly Gln Thr Pro Glu Thr Leu Gln Ser Leu Gln Thr Gln  
 100 105 110  
 Leu Lys Ala Gln Asn Ser Lys Ile Gln Gln Leu Phe Gln Lys Val Ala  
 115 120 125  
 Gln Gln Gln Arg Tyr Leu Ser Lys Gln Asn Leu Arg Ile Gln Asn Leu  
 130 135 140  
 Gln Ser Gln Ile Asp Leu Leu Ala Pro Thr His Leu Asp Asn Gly Val  
 145 150 155 160  
 Asp Lys Thr Ser Arg Gly Lys Lys Leu Ser Lys Met Thr Gln Leu Ile  
 165 170 175  
 Gly Leu Thr Ser Asn Ala Thr His Leu His Arg Pro Ala Arg Asp Cys  
 180 185 190  
 Gln Glu Leu Phe Gln Glu Gly Glu Arg His Ser Gly Leu Phe Gln Ile  
 195 200 205  
 Gln Pro Leu Gly Ser Pro Pro Phe Leu Val Asn Cys Glu Met Thr Ser  
 210 215 220

Asp Gly Gly Trp Thr Val Ile Gln Arg Arg Leu Asn Gly Ser Val Asp  
 225 230 235 240  
 Phe Asn Gln Ser Trp Glu Ala Tyr Lys Asp Gly Phe Gly Asp Pro Gln  
 245 250 255  
 Gly Glu Phe Trp Leu Gly Leu Glu Lys Met His Ser Ile Thr Gly Asp  
 260 265 270  
 Arg Gly Ser Gln Leu Ala Val Gln Leu Gln Asp Trp Asp Gly Asn Ala  
 275 280 285  
 Lys Leu Leu Gln Phe Pro Ile His Leu Gly Gly Glu Asp Thr Ala Tyr  
 290 295 300  
 Ser Leu Gln Leu Thr Glu Pro Thr Ala Asn Glu Leu Gly Ala Thr Asn  
 305 310 315 320  
 Val Ser Pro Asn Gly Leu Ser Leu Pro Phe Ser Thr Trp Asp Gln Asp  
 325 330 335  
 His Asp Leu Arg Gly Asp Leu Asn Cys Ala Lys Ser Leu Ser Gly Gly  
 340 345 350  
 Trp Trp Phe Gly Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe  
 355 360 365  
 His Ser Ile Pro Arg Gln Arg Gln Glu Arg Lys Lys Gly Ile Phe Trp  
 370 375 380  
 Lys Thr Trp Lys Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Leu Leu  
 385 390 395 400  
 Ile Gln Pro Met Glu Ala Thr Ala Ala Ser  
 405 410

<210> 118  
 <211> 406  
 <212> PRT  
 <213> Homo sapiens

<400> 118

Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala  
 1 5 10 15  
 Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser  
 50 55 60  
 Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys  
 65 70 75 80  
 Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg  
 85 90 95  
 Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln  
 100 105 110  
 Asn Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg  
 115 120 125  
 His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe  
 130 135 140  
 Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala  
 145 150 155 160  
 Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His  
 165 170 175  
 Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe  
 180 185 190  
 Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly  
 195 200 205  
 Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp



210 215 220  
 Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro  
 225 230 235 240  
 Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp  
 245 250 255  
 Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg  
 260 265 270  
 Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln  
 275 280 285  
 Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu  
 290 295 300  
 Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser  
 305 310 315 320  
 Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg  
 325 330 335  
 Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly  
 340 345 350  
 Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro  
 355 360 365  
 Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg  
 370 375 380  
 Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met  
 385 390 395 400  
 Ala Ala Glu Ala Ala Ser  
 405

<210> 119  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

<400> 119

Met Trp Gln Ile Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala  
 1 5 10 15  
 Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys  
 20 25 30  
 Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro  
 35 40 45  
 Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala  
 50 55 60  
 Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu  
 65 70 75 80  
 Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys  
 85 90 95

<210> 120  
 <211> 13  
 <212> PRT  
 <213> Gallus gallus

<400> 120

Met Lys Lys Glu Met Val Glu Ile Gln Gln Asn Ala Val  
1 5 10

<210> 121  
 <211> 441  
 <212> PRT  
 <213> Gallus gallus

<400> 121

Met Arg Leu Ser Val Tyr Phe Thr Trp Gly Cys Ser Ile Val Leu Ala  
 1 5 10 15  
 Ala Gly Tyr Asn Ala Phe Gly Lys Gly Ala Glu Pro Ala Gly Lys Lys

20					25					30					
Gln	Tyr	Gln	Val	Gln	His	Gly	Pro	Cys	Ser	Tyr	Thr	Phe	Leu	Leu	Pro
		35					40					45			
Glu	Ala	Asp	Ser	Cys	Arg	Pro	Pro	Tyr	Val	Pro	Asn	Ala	Val	Gln	Arg
	50					55					60				
Asp	Ala	Pro	Leu	Asp	Tyr	Asp	Asp	Ser	Val	Gln	Arg	Leu	Gln	Leu	Leu
65					70					75					80
Glu	Asn	Ile	Met	Glu	Asn	Asn	Thr	Gln	Trp	Leu	Leu	Lys	Val	Leu	Asn
				85					90					95	
Gln	Thr	Thr	Arg	Leu	Glu	Leu	Gln	Leu	Leu	Glu	His	Ser	Leu	Ser	Thr
			100					105					110		
Asn	Lys	Leu	Glu	Arg	Gln	Ile	Ser	Val	Gln	Thr	Asn	Glu	Ile	Thr	Lys
		115					120					125			
Leu	Gln	Glu	Lys	Asn	Ser	Phe	Leu	Glu	Lys	Arg	Val	Leu	Glu	Met	Glu
	130					135					140				
Asp	Lys	His	Thr	Leu	Gln	Leu	Lys	Ser	Ile	Lys	Asp	Glu	Lys	Asp	Gln
145					150					155					160
Leu	Gln	Val	Leu	Val	Ala	Arg	Gln	Asn	Ser	Ile	Ile	Glu	Glu	Leu	Glu
				165					170					175	
Lys	Gln	Leu	Val	Thr	Ala	Thr	Val	Asn	Asn	Ser	Val	Leu	Gln	Lys	Gln
			180					185					190		
Gln	His	Asp	Leu	Met	Glu	Thr	Val	His	Asn	Leu	Leu	Thr	Met	Ile	Ser
		195					200					205			
Thr	Pro	Asn	Ser	Ala	Lys	Lys	Asn	Phe	Ile	Ala	Lys	Glu	Glu	Gln	Ile
	210					215					220				
Ser	Phe	Lys	Asp	Cys	Ala	Glu	Ala	Phe	Lys	Ser	Gly	Leu	Thr	Thr	Ser
225					230					235					240
Gly	Ile	Tyr	Thr	Leu	Thr	Phe	Pro	Asn	Ser	Ala	Gln	Glu	Lys	Lys	Ala
				245					250					255	
Tyr	Cys	Asp	Met	Glu	Ser	Asn	Gly	Gly	Gly	Trp	Thr	Val	Leu	Gln	Arg
			260					265					270		
Arg	Glu	Asp	Gly	Ser	Val	Asp	Phe	His	Arg	Thr	Trp	Lys	Glu	Tyr	Lys
		275					280					285			
Ile	Gly	Phe	Gly	Asp	Pro	Ala	Gly	Glu	Tyr	Trp	Leu	Gly	Asn	Glu	Phe
	290					295					300				
Val	Ser	Gln	Leu	Thr	Asn	Gln	Lys	Arg	Tyr	Val	Leu	Lys	Ile	Ile	Leu
305					310					315					320
Lys	Asp	Trp	Glu	Gly	Asn	Glu	Ala	Tyr	Thr	Leu	Tyr	Asp	Gln	Phe	Tyr
				325					330					335	
Leu	Ala	Asn	Glu	Glu	Gln	Lys	Tyr	Arg	Ile	His	Leu	Lys	Gly	Leu	Thr
			340					345					350		
Gly	Thr	Ala	Gly	Lys	Ile	Ser	Ser	Ile	Ser	Gln	Pro	Gly	Asn	Asp	Phe
		355					360					365			
Ser	Thr	Lys	Asp	Ala	Asp	Asn	Asp	Lys	Cys	Ile	Cys	Lys	Cys	Ser	Gln
	370					375					380				
Met	Leu	Thr	Gly	Gly	Trp	Trp	Phe	Asp	Ala	Cys	Gly	Pro	Ser	Asn	Leu
385					390					395					400
Asn	Gly	Met	Tyr	Tyr	Pro	Leu	Arg	Gln	Asn	Asn	Asn	Lys	Phe	Asn	Gly
				405					410					415	
Ile	Lys	Trp	Tyr	Tyr	Trp	Lys	Gly	Ser	Gly	Tyr	Ser	Leu	Lys	Ala	Thr
			420					425					430		
Thr	Met	Met	Ile	Arg	Pro	Ala	Asp	Phe							
		435					440								

<210> 122  
 <211> 444  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 122

Met Trp Gln Ile Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala  
 1 5 10 15  
 Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys  
 20 25 30  
 Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro  
 35 40 45  
 Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala  
 50 55 60  
 Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu  
 65 70 75 80  
 Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys  
 85 90 95  
 Val Leu Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu Leu Glu His Ser  
 100 105 110  
 Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp Gln Thr Ser Glu  
 115 120 125  
 Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu Lys Lys Val Leu  
 130 135 140  
 Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser Ile Lys Glu Glu  
 145 150 155 160  
 Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn Ser Ile Ile Glu  
 165 170 175  
 Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn Asn Ser Val Leu  
 180 185 190  
 Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn Asn Leu Leu Thr  
 195 200 205  
 Met Met Ser Thr Ser Asn Ser Ala Lys Asp Pro Thr Val Ala Lys Glu  
 210 215 220  
 Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe Lys Ser Gly His  
 225 230 235 240  
 Thr Thr Asn Gly Ile Tyr Thr Leu Thr Phe Pro Asn Ser Thr Glu Glu  
 245 250 255  
 Ile Lys Ala Tyr Cys Asp Met Glu Ala Gly Gly Gly Gly Trp Thr Ile  
 260 265 270  
 Ile Gln Arg Arg Glu Asp Gly Ser Val Asp Phe Gln Arg Thr Trp Lys  
 275 280 285  
 Glu Tyr Lys Val Gly Phe Gly Asn Pro Ser Gly Glu Tyr Trp Leu Gly  
 290 295 300  
 Asn Glu Phe Val Ser Gln Leu Thr Asn Gln Gln Arg Tyr Val Leu Lys  
 305 310 315 320  
 Ile His Leu Lys Asp Trp Glu Gly Asn Glu Ala Tyr Ser Leu Tyr Glu  
 325 330 335  
 His Phe Tyr Leu Ser Ser Glu Glu Leu Asn Tyr Arg Ile His Leu Lys  
 340 345 350  
 Gly Leu Thr Gly Thr Ala Gly Lys Ile Ser Ser Ile Ser Gln Pro Gly  
 355 360 365  
 Asn Asp Phe Ser Thr Lys Asp Gly Asp Asn Asp Lys Cys Ile Cys Lys  
 370 375 380  
 Cys Ser Gln Met Leu Thr Gly Gly Trp Trp Phe Asp Ala Cys Gly Pro  
 385 390 395 400  
 Ser Asn Leu Asn Gly Met Tyr Tyr Pro Gln Arg Gln Asn Thr Asn Lys  
 405 410 415  
 Phe Asn Gly Ile Lys Trp Tyr Tyr Trp Lys Gly Ser Gly Tyr Ser Leu  
 420 425 430

Lys Ala Thr Thr Met Met Ile Arg Pro Ala Asp Phe  
 435 440  
 <210> 123  
 <211> 406  
 <212> PRT  
 <213> Homo sapiens  
 <400> 123  
 Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala  
 1 5 10 15  
 Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser  
 20 25 30  
 Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu  
 35 40 45  
 Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser  
 50 55 60  
 Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys  
 65 70 75 80  
 Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg  
 85 90 95  
 Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln  
 100 105 110  
 Asn Asn Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg  
 115 120 125  
 His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe  
 130 135 140  
 Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala  
 145 150 155 160  
 Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His  
 165 170 175  
 Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe  
 180 185 190  
 Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly  
 195 200 205  
 Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp  
 210 215 220  
 Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro  
 225 230 235 240  
 Trp Glu Thr Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp  
 245 250 255  
 Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg  
 260 265 270  
 Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln  
 275 280 285  
 Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu  
 290 295 300  
 Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser  
 305 310 315 320  
 Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg  
 325 330 335  
 Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly  
 340 345 350  
 Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro  
 355 360 365  
 Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg  
 370 375 380  
 Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met  
 385 390 395 400

Ala Ala Glu Ala Ala Ser  
405

<210> 124  
<211> 363  
<212> PRT  
<213> Homo sapiens

<400> 124

Met Arg Pro Leu Cys Val Thr Cys Trp Trp Leu Gly Leu Leu Ala Ala  
1 5 10 15

Met Gly Ala Val Ala Gly Gln Glu Asp Gly Phe Glu Gly Thr Glu Glu  
20 25 30

Gly Ser Pro Arg Glu Phe Ile Tyr Leu Asn Arg Tyr Lys Arg Ala Gly  
35 40 45

Glu Ser Gln Asp Lys Cys Thr Tyr Thr Phe Ile Val Pro Gln Gln Arg  
50 55 60

Val Thr Gly Ala Ile Cys Val Asn Ser Lys Glu Pro Glu Val Leu Leu  
65 70 75 80

Glu Asn Arg Val His Lys Gln Glu Leu Glu Leu Leu Asn Asn Glu Leu  
85 90 95

Leu Lys Gln Lys Arg Gln Ile Glu Thr Leu Gln Gln Leu Val Lys Val  
100 105 110

Asp Gly Gly Ile Val Ser Glu Val Lys Leu Leu Arg Lys Glu Ser Arg  
115 120 125

Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu  
130 135 140

Ile Ile Arg Lys Arg Asp Asn Ala Leu Glu Leu Ser Gln Leu Glu Asn  
145 150 155 160

Arg Ile Leu Asn Gln Thr Ala Asp Met Leu Gln Leu Ala Ser Lys Tyr  
165 170 175

Lys Asp Leu Glu His Lys Tyr Gln His Leu Ala Thr Leu Ala His Asn  
180 185 190

Gln Ser Glu Ile Ile Ala Gln Leu Glu Glu His Cys Gln Arg Val Pro  
195 200 205

Ser Ala Arg Pro Val Pro Gln Pro Pro Pro Ala Ala Pro Pro Arg Val  
210 215 220

Tyr Gln Pro Pro Thr Tyr Asn Arg Ile Ile Asn Gln Ile Ser Thr Asn  
225 230 235 240

Glu Ile Gln Ser Asp Gln Asn Leu Lys Val Leu Pro Pro Pro Leu Pro  
245 250 255

Thr Met Pro Thr Leu Thr Ser Leu Pro Ser Ser Thr Asp Lys Pro Ser  
260 265 270

Gly Pro Trp Arg Asp Cys Leu Gln Ala Leu Glu Asp Gly His Asp Thr  
275 280 285

Ser Ser Ile Tyr Leu Val Lys Pro Glu Asn Thr Asn Arg Leu Met Gln  
290 295 300

Val Trp Cys Asp Gln Arg His Asp Pro Gly Gly Trp Thr Val Ile Gln  
305 310 315 320

Arg Arg Leu Asp Gly Ser Val Asn Phe Phe Arg Asn Trp Glu Thr Tyr  
325 330 335

Lys Gln Gly Phe Gly Asn Ile Asp Gly Glu Tyr Trp Leu Gly Leu Glu  
340 345 350

Asn Ile Tyr Trp Leu Thr Asn Gln Gln Arg Ser  
355 360

<210> 125  
<211> 2336  
<212> DNA  
<213> Homo sapiens

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<400> 125
atctgggtca gctgcagctg gttactgcat ttctccatgt ggcagacaga gcaaagccac 60
aacgctttct ctgctggatt aaagacggcc cacagaccag aacttccact atactactta 120
aaattacata ggtggcttgt caaattcaat tgattagtat tgtaaaagga aaaagaagtt 180
ccttcttaca gcttggattc acggtccaaa acaaaaatgc agctgccatt aaagtcacag 240
atgaacaaac ttctacactg atttttaaaa tcaagaataa gggcagcaag tttctggatt 300
cactgaatca acagacacaa aaagacatca ttttacaacc tcatttcaaa atgaagactt 360
ttacctggac cctaggtgtg ctattcttcc tactagtga cactggacat tgcagagggtg 420
gacaattcaa aattaaaaaa ataaccaga gaagataccc tcgtgccaca gatggtaaag 480
aggaagcaaa gaaatgtgca tacacattcc tggtagctga ccaaagaata acagggccaa 540
tctgtgtcaa caccaagggg caagatgcaa gtaccattaa agacatgatc accaggatgg 600
accttgaaaa cctgaaggat gtgctctcca ggcagaagcg ggagatagat gttctgcaac 660
tgggtgggtga ttagatgga aacattgtga atgaggtaaa gctgctgaga aaggaaagcc 720
gtaacatgaa ctctcgtgtt actcaactct atatgcaatt attacatgag attatccgta 780
agagggataa ttcacttgaa ctttcccaac tggaaaacaa aatcctcaat gtcaccacag 840
aaatgttgaa gatggcaaca agatacaggg aactagaggt gaaatacgct tccttgactg 900
atcttgtcaa taaccaatct gtgatgatca ctttgttggg agaacagtgc ttgaggatat 960
tttcccgaca agacacccat gtgtctcccc cacttgtcca ggtggtgcca caacatattc 1020
ctaacagcca acagtatact cctggtctgc tgggaggtaa cgagattcag agggatccag 1080
gttatccag agatttaatg ccaccacctg atctggcaac ttctcccacc aaaagccctt 1140
tcaagatacc accggtaact ttcatacatg aaggaccatt caaagactgt cagcaagcaa 1200
aagaagctgg gcattcggtc agtggattta tatgattaaa cctgaaaaca gcaatggacc 1260
aatgcagtta tgggtgtgaaa acagtttggg ccctgggggt tggactgtta ttcagaaaag 1320
aacagacggc tctgtcaact tcttcagaaa ttgggaaaat tataagaaag ggtttggaag 1380
cattgacgga gaatactggc ttggactgga aaatatctat atcgtttagc atcaagataa 1440
ttacaagtta ttgattgaat tagaagactg gagtgataaa aaagtctatg cagaatacag 1500
cagctttcgt ctggaacctg aaagtgaatt ctatagactg cgcctgggaa cttaccaggg 1560
aaatgcaggg gattctatga tgtggcataa tggtaaacga cagagataaa gatatgtatg 1620
caggaaactg cgccacttt cataaaggag gctggtggta caatgcctgt gcacattcta 1680
gcctaaatgg agtatggtac agaggaggcc attacagaag caagcaccaa gatggaattt 1740
tctgggccga atacagaggc gggtcatact ccttaagagc agttcagatg atgatcaagc 1800
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<210> 128  
 <211> 461  
 <212> PRT  
 <213> Homo sapiens

<400> 128

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 20 25 30  
 Cys Thr Val Leu Leu Ala Leu Ala Val Leu Leu Ala Val Ala Val Thr  
 35 40 45  
 Gly Ala Val Leu Phe Leu Asn His Ala His Ala Pro Gly Thr Ala Pro  
 50 55 60  
 Pro Pro Val Val Ser Thr Gly Ala Ala Ser Ala Asn Ser Ala Leu Val  
 65 70 75 80  
 Thr Val Glu Arg Ala Asp Ser Ser His Leu Ser Ile Leu Ile Asp Pro  
 85 90 95  
 Arg Cys Pro Asp Leu Thr Asp Ser Phe Ala Arg Leu Glu Ser Ala Gln  
 100 105 110  
 Ala Ser Val Leu Gln Ala Leu Thr Glu His Gln Ala Gln Pro Arg Leu  
 115 120 125  
 Val Gly Asp Gln Glu Gln Glu Leu Leu Asp Thr Leu Ala Asp Gln Leu  
 130 135 140  
 Pro Arg Leu Leu Ala Arg Ala Ser Glu Leu Gln Thr Glu Cys Met Gly  
 145 150 155 160  
 Leu Arg Lys Gly His Gly Thr Leu Gly Gln Gly Leu Ser Ala Leu Gln

165 170 175  
 Ser Glu Gln Gly Arg Leu Ile Gln Leu Leu Ser Glu Ser Gln Gly His  
 180 185 190  
 Met Ala His Leu Val Asn Ser Val Ser Asp Ile Leu Asp Ala Leu Gln  
 195 200 205  
 Arg Asp Arg Gly Leu Gly Arg Pro Arg Asn Lys Ala Asp Leu Gln Arg  
 210 215 220  
 Ala Pro Ala Arg Gly Thr Arg Pro Arg Gly Cys Ala Thr Gly Ser Arg  
 225 230 235 240  
 Pro Arg Asp Cys Leu Asp Val Leu Leu Ser Gly Gln Gln Asp Asp Gly  
 245 250 255  
 Val Tyr Ser Val Phe Pro Thr His Tyr Pro Ala Gly Phe Gln Val Tyr  
 260 265 270  
 Cys Asp Met Arg Thr Asp Gly Gly Gly Trp Thr Val Phe Gln Arg Arg  
 275 280 285  
 Glu Asp Gly Ser Val Asn Phe Phe Arg Gly Trp Asp Ala Tyr Arg Asp  
 290 295 300  
 Gly Phe Gly Arg Leu Thr Gly Glu His Trp Leu Gly Leu Lys Arg Ile  
 305 310 315 320  
 His Ala Leu Thr Thr Gln Ala Ala Tyr Glu Leu His Val Asp Leu Glu  
 325 330 335  
 Asp Phe Glu Asn Gly Thr Ala Tyr Ala Arg Tyr Gly Ser Phe Gly Val  
 340 345 350  
 Gly Leu Phe Ser Val Asp Pro Glu Glu Asp Gly Tyr Pro Leu Thr Val  
 355 360 365  
 Ala Asp Tyr Ser Gly Thr Ala Gly Asp Ser Leu Leu Lys His Ser Gly  
 370 375 380  
 Met Arg Phe Thr Thr Lys Asp Arg Asp Ser Asp His Ser Glu Asn Asn  
 385 390 395 400  
 Cys Ala Ala Phe Tyr Arg Gly Ala Trp Trp Tyr Arg Asn Cys His Thr  
 405 410 415  
 Ser Asn Leu Asn Gly Gln Tyr Leu Arg Gly Ala His Ala Ser Tyr Ala  
 420 425 430  
 Asp Gly Val Glu Trp Ser Ser Trp Thr Gly Trp Gln Tyr Ser Leu Lys  
 435 440 445  
 Phe Ser Glu Met Lys Ile Arg Pro Val Arg Glu Asp Arg  
 450 455 460  
 <210> 129  
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 <212> PRT  
 <213> Homo sapiens  
 <400> 129  
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 20 25 30  
 Pro Lys Ser Arg Phe Ala Met Leu Asp Asp Val Lys Ile Leu Ala Asn  
 35 40 45  
 Gly Leu Leu Gln Leu Gly His Gly Leu Lys Asp Phe Val His Lys Thr  
 50 55 60  
 Lys Gly Gln Ile Asn Asp Ile Phe Gln Lys Leu Asn Ile Phe Asp Gln  
 65 70 75 80  
 Ser Phe Tyr Asp Leu Ser Leu Gln Thr Ser Glu Ile Lys Glu Glu Glu  
 85 90 95  
 Lys Glu Leu Arg Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu  
 100 105 110



Val Lys Asn Met Ser Leu Glu Leu Asn Ser Lys Leu Glu Ser Leu Leu  
 115 120 125  
 Glu Glu Lys Ile Leu Leu Gln Gln Lys Val Lys Tyr Leu Glu Glu Gln  
 130 135 140  
 Leu Thr Asn Leu Ile Gln Asn Gln Pro Glu Thr Pro Glu His Pro Glu  
 145 150 155 160  
 Val Thr Ser Leu Lys Thr Phe Val Glu Lys Gln Asp Asn Ser Ile Lys  
 165 170 175  
 Asp Leu Leu Gln Thr Val Glu Asp Gln Tyr Lys Gln Leu Asn Gln Gln  
 180 185 190  
 His Ser Gln Ile Lys Glu Ile Glu Asn Gln Leu Arg Arg Thr Ser Ile  
 195 200 205  
 Gln Glu Pro Thr Glu Ile Ser Leu Ser Ser Lys Pro Arg Ala Pro Arg  
 210 215 220  
 Thr Thr Phe Phe Leu Gln Leu Asn Glu Ile Arg Asn Val Lys His Asp  
 225 230 235 240  
 Gly Ile Pro Ala Glu Cys Thr Thr Ile Tyr Asn Arg Gly Glu His Thr  
 245 250 255  
 Ser Gly Met Tyr Ala Ile Arg Pro Ser Asn Ser Gln Val Phe Gly Val  
 260 265 270  
 Tyr Cys Asp Val Ile Ser Gly Ser Pro Trp Thr Leu Ile Gln His Arg  
 275 280 285  
 Ile Asp Gly Ser Gln Asn Phe Asn Glu Thr Trp Glu Asn Tyr Lys Tyr  
 290 295 300  
 Gly Phe Gly Arg Leu Asp Gly Glu Phe Trp Leu Gly Leu Glu Lys Ile  
 305 310 315 320  
 Tyr Ser Ile Val Lys Gln Ser Asn Tyr Val Leu Arg Ile Glu Leu Glu  
 325 330 335  
 Asp Trp Lys Asp Asn Lys His Tyr Ile Glu Tyr Ser Phe Tyr Leu Gly  
 340 345 350  
 Asn His Glu Thr Asn Tyr Thr Leu His Leu Val Ala Ile Thr Gly Asn  
 355 360 365  
 Val Pro Asn Ala Ile Pro Glu Asn Lys Asp Leu Val Phe Ser Thr Trp  
 370 375 380  
 Asp His Lys Ala Lys Gly His Phe Asn Cys Pro Glu Gly Tyr Ser Gly  
 385 390 395 400  
 Gly Trp Trp Trp His Asp Glu Cys Gly Glu Asn Asn Leu Asn Gly Lys  
 405 410 415  
 Tyr Asn Lys Pro Arg Ala Lys Ser Lys Pro Glu Arg Arg Arg Gly Leu  
 420 425 430  
 Ser Trp Lys Ser Gln Asn Gly Arg Leu Tyr Ser Ile Lys Ser Thr Lys  
 435 440 445  
 Met Leu Ile His Pro Thr Asp Ser Glu Ser Phe Glu  
 450 455 460

<210> 130  
 <211> 494  
 <212> PRT  
 <213> Homo sapiens

<400> 130

Met Arg Pro Leu Cys Val Thr Cys Trp Trp Leu Gly Leu Leu Ala Ala  
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 Met Gly Ala Val Ala Gly Gln Glu Asp Gly Phe Glu Gly Thr Glu Glu  
 20 25 30  
 Gly Ser Pro Arg Glu Phe Ile Tyr Leu Asn Arg Tyr Lys Arg Ala Gly  
 35 40 45  
 Glu Ser Gln Asp Lys Cys Thr Tyr Thr Phe Ile Val Pro Gln Gln Arg  
 50 55 60

Val Thr Gly Ala Ile Cys Val Asn Ser Lys Glu Pro Glu Val Leu Leu  
 65 70 75 80  
 Glu Asn Arg Val His Lys Gln Glu Leu Glu Leu Leu Asn Asn Glu Leu  
 85 90 95  
 Leu Lys Gln Lys Arg Gln Ile Glu Thr Leu Gln Gln Leu Val Glu Val  
 100 105 110  
 Asp Gly Gly Ile Val Ser Glu Val Lys Leu Leu Arg Lys Glu Ser Arg  
 115 120 125  
 Asn Met Asn Ser Arg Val Thr Gln Leu Tyr Met Gln Leu Leu His Glu  
 130 135 140  
 Ile Ile Arg Lys Arg Asp Asn Ala Leu Glu Leu Ser Gln Leu Glu Asn  
 145 150 155 160  
 Arg Ile Leu Asn Gln Thr Ala Asp Met Leu Gln Leu Ala Ser Lys Tyr  
 165 170 175  
 Lys Asp Leu Glu His Lys Tyr Gln His Leu Ala Thr Leu Ala His Asn  
 180 185 190  
 Gln Ser Glu Ile Ile Ala Gln Leu Glu Glu His Cys Gln Arg Val Pro  
 195 200 205  
 Ser Ala Arg Pro Val Pro Gln Pro Pro Pro Ala Ala Pro Pro Arg Val  
 210 215 220  
 Tyr Gln Pro Pro Thr Tyr Asn Arg Ile Ile Asn Gln Ile Ser Thr Asn  
 225 230 235 240  
 Glu Ile Gln Ser Asp Gln Asn Leu Lys Val Leu Pro Pro Pro Leu Pro  
 245 250 255  
 Thr Met Pro Thr Leu Thr Ser Leu Pro Ser Ser Thr Asp Lys Pro Ser  
 260 265 270  
 Gly Pro Trp Arg Asp Cys Leu Gln Ala Leu Glu Ser Gly His Asp Thr  
 275 280 285  
 Ser Ser Ile Tyr Leu Val Lys Pro Glu Asn Thr Asn Arg Leu Met Gln  
 290 295 300  
 Val Trp Cys Asp Gln Arg His Asp Pro Gly Gly Trp Thr Val Ile Gln  
 305 310 315 320  
 Arg Arg Leu Asp Gly Ser Val Asn Phe Phe Arg Asn Trp Glu Thr Trp  
 325 330 335  
 Lys Gln Gly Phe Gly Asn Ile Asp Gly Glu Tyr Trp Leu Gly Leu Glu  
 340 345 350  
 Asn Ile Tyr Trp Leu Thr Asn Gln Gly Asn Tyr Lys Leu Leu Val Thr  
 355 360 365  
 Met Glu Asp Trp Ser Gly Arg Lys Val Phe Ala Glu Tyr Ala Ser Phe  
 370 375 380  
 Arg Leu Glu Pro Glu Ser Glu Tyr Tyr Lys Leu Arg Leu Gly Arg Tyr  
 385 390 395 400  
 His Gly Asn Ala Gly Asp Ser Phe Thr Trp His Asn Gly Lys Gln Phe  
 405 410 415  
 Thr Thr Leu Asp Arg Asp His Asp Val Tyr Thr Gly Asn Ala Cys Ala  
 420 425 430  
 His Tyr Gln Lys Gly Gly Trp Trp Tyr Asn Ala Cys Ala His Ser Asn  
 435 440 445  
 Leu Asn Gly Val Trp Tyr Arg Gly Gly His Tyr Arg Ser Arg Tyr Gln  
 450 455 460  
 Asp Gly Val Tyr Trp Ala Glu Phe Arg Gly Gly Ser Tyr Ser Leu Lys  
 465 470 475 480  
 Lys Val Val Met Met Ile Arg Pro Asn Pro Asn Thr Phe His  
 485 490

&lt;210&gt; 131

&lt;211&gt; 405

<212> PRT  
 <213> Homo sapiens

<400> 131

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Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser
20      25      30
Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu
35      40      45
Leu Gln Leu Gly Gln Gly Cys Ala Asn Thr Gly Ala His Pro Gln Ser
50      55      60
Ala Glu Arg Ala Gly Ala Arg Leu Ser Ala Cys Gly Ser Ala Cys Gln
65      70      75      80
Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg Val
85      90      95
Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln Asn
100     105     110
Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg His
115     120     125
Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe Gly
130     135     140
Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala Arg
145     150     155     160
Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His Asn
165     170     175
Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe Gln
180     185     190
Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly Ser
195     200     205
Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp Thr
210     215     220
Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro Trp
225     230     235     240
Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp Leu
245     250     255
Gly Leu Glu Lys Val His Ser Met Met Gly Asp Arg Asn Ser Arg Leu
260     265     270
Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln Phe
275     280     285
Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu Thr
290     295     300
Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser Gly
305     310     315     320
Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg Arg
325     330     335
Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly Thr
340     345     350
Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro Gln
355     360     365
Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg Gly
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Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met Ala
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Ala Glu Ala Ala Ser
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<210> 132

<211> 412  
 <212> PRT  
 <213> Homo sapiens

<400> 132

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20      25      30
Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Leu Leu Ala His Gly Leu
35      40      45
Leu Gln Leu Gly His Gly Leu Arg Glu His Val Glu Arg Thr Arg Gly
50      55      60
Gln Leu Gly Ala Leu Glu Arg Arg Met Ala Ala Cys Gly Asn Ala Cys
65      70      75      80
Gln Gly Pro Lys Gly Lys Asp Ala Pro Phe Lys Asp Ser Glu Asp Arg
85      90      95
Val Pro Glu Gly Gln Thr Pro Glu Thr Leu Gln Ser Leu Gln Thr Gln
100     105     110
Leu Lys Ala Gln Asn Ser Lys Ile Gln Gln Leu Phe Gln Lys Val Ala
115     120     125
Gln Gln Gln Arg Tyr Leu Ser Lys Gln Asn Leu Arg Ile Gln Asn Leu
130     135     140
Gln Ser Gln Ile Asp Leu Leu Ala Pro Thr His Leu Asp Asn Gly Val
145     150     155     160
Asp Lys Thr Ser Arg Gly Lys Arg Leu Pro Lys Met Thr Gln Leu Ile
165     170     175
Gly Leu Thr Pro Asn Ala Ala Thr His Leu His Arg Pro Pro Arg Asp
180     185     190
Cys Gln Glu Leu Phe Gln Glu Gly Glu Arg His Ser Gly Leu Phe Gln
195     200     205
Ile Gln Pro Leu Gly Ser Pro Pro Phe Leu Val Asn Cys Glu Met Thr
210     215     220
Ser Asp Gly Gly Trp Thr Val Ile Gln Arg Arg Leu Asn Gly Ser Val
225     230     235     240
Asp Phe Asn Gln Ser Trp Glu Ala Tyr Lys Asp Gly Phe Gly Asp Pro
245     250     255
Gln Gly Glu Phe Trp Leu Gly Leu Glu Lys Met His Ser Ile Thr Gly
260     265     270
Asn Arg Gly Ser Gln Leu Ala Val Gln Leu Gln Asp Trp Asp Gly Asn
275     280     285
Ala Lys Leu Leu Gln Phe Pro Ile His Leu Gly Gly Glu Asp Thr Ala
290     295     300
Tyr Ser Leu Gln Leu Thr Glu Pro Thr Ala Asn Glu Leu Gly Ala Thr
305     310     315     320
Asn Val Ser Pro Asn Gly Leu Ser Leu Pro Phe Ser Thr Trp Asp Gln
325     330     335
Asp His Asp Leu Arg Gly Asp Leu Asn Cys Ala Lys Ser Leu Ser Gly
340     345     350
Gly Trp Trp Phe Gly Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr
355     360     365
Phe His Ser Ile Pro Arg Gln Arg Gln Glu Arg Lys Lys Gly Ile Phe
370     375     380
Trp Lys Thr Trp Lys Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Leu
385     390     395     400
Leu Ile Gln Pro Met Glu Ala Thr Ala Ala Ala Ser
405     410

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<210> 133  
 <211> 756  
 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (543)..(543)  
 <223> "n" may be any nucleotide.

<220>  
 <221> misc feature  
 <222> (612)..(612)  
 <223> "n" may be any nucleotide.

<220>  
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 <222> (690)..(690)  
 <223> "n" may be any nucleotide.

<220>  
 <221> misc feature  
 <222> (693)..(693)  
 <223> "n" may be any nucleotide.

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 acagtgtctca gaagaatgca gttccaagat gatctgtatt gtataacata agtgttctgt 120  
 tttccagtta ttactgata aacttgacaca taacattctt ggttttgaca gcagcgtctg 180  
 taaactgtca gtctgattct cagcctcggg gttcatcttt gcatagggtg tctgtctaata 240  
 cacaattatg gatgtttagg gtcttgcttt ggtccgttaa gtgatgcaag ttttaagtgt 300  
 aaagtttaca ggctctaatac tggagcatgt ggggtccgctc agcaccgagc acacgccttc 360  
 tgtggtggaa gaggacacag tgcgcagccg tgactttcag tgcactgggc ttaagtcttt 420  
 gaaaatagtt cgagacagtt cctcaggtgg actgggatgt ttagaaatct gctggtcggg 480  
 tcaatcatgt tgtggccttg agcgaatagc ctgagccttt ccagtagtac catttaatgc 540  
 cgntgaactt tatttgtgtc tggctctgtg gatagtacat tccggtcaag ttggaaggac 600  
 cacatgcac anaccaccag gctattaatg agttctcact tgagagatta gaatgttcat 660  
 acaatgagta agcctcatc ccttaccagn ctnttaggtg attttagcac atagcgttgc 720  
 tgattagtcg ttgcgaacca actcatttcc cagcca 756

<210> 134  
 <211> 530  
 <212> DNA  
 <213> Homo sapiens

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 gttctgaggt tgcttttatt ccaagaactc tgtgagctcc gccagatac cattggcgcc 60  
 tgcttgtgtc ccaggggac ctacacacaa cagcaccagc accatgaggg cgctctcgac 120  
 ccacacaagc cctgggtccc gtcagtcaat gtgactgagt ccgccattga ggccagtctg 180  
 gctttgcaga tgctgaattc gcagggtgctg cttctccagg tgccgctgct gctgggccac 240  
 cttgtggaag agttgctgga tctgtctgtt ctgagccttg agttgtgtct gcaggctgtg 300  
 aaggacctca gggccaccc ggctctcagg ggctaacggg aggtcgggtg acccctcgg 360  
 tccctgacag gcggacccgc acgcgctcag gcgccgtttc agcgcgctca gctgactgcg 420  
 ggtgcgctcc gcgtgttcgc gcagcccctg gccgagctgc aggagtccgt gcgccaggac 480  
 attcatctcg tcccaggacg caaagcgcgg cgacttggac tgcacgggtc 530

<210> 135  
 <211> 458  
 <212> DNA  
 <213> Homo sapiens

<400> 135  
 tttttttttt tttttttgtt ctgaggttgc ttttattcca agaactctgt gagtccgcc 60

cagataccat tggcgctgc ttgtgtcccc aggggaccta cacacaacag caccagcacc 120  
 atgagggcgc tctcgaccca cacaagccct ggtccccgtc agtcaatgtg actgagtccg 180  
 ccattgaggc cagtctggct ttgcagatgc tgaattcgca ggtgctgctt ctccaggtgc 240  
 cgctgctgct gggccacctt gtggaagagt tgctggatcc tgctgttctg agccttgagt 300  
 tgtgtctgca ggctgtgaag gacctcaggg tccaccggc tctcaggggc taacgggagg 360  
 tcgggtggacc cctcggttcc ctgacaggcg gaccgcacg cgctcaggcg ccgctccagc 420  
 gcgctcagct gactgcgggt gcgctccgcg tgttcgcg 458

<210> 136  
 <211> 2201  
 <212> PRT  
 <213> Homo sapiens

<400> 136

Met Gly Ala Met Thr Gln Leu Leu Ala Gly Val Phe Leu Ala Phe Leu  
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 Ala Leu Ala Thr Glu Gly Gly Val Leu Lys Lys Val Ile Arg His Lys  
 20 25 30  
 Arg Gln Ser Gly Val Asn Ala Thr Leu Pro Glu Glu Asn Gln Pro Val  
 35 40 45  
 Val Phe Asn His Val Tyr Asn Ile Lys Leu Pro Val Gly Ser Gln Cys  
 50 55 60  
 Ser Val Asp Leu Glu Ser Ala Ser Gly Glu Lys Asp Leu Ala Pro Pro  
 65 70 75 80  
 Ser Glu Pro Ser Glu Ser Phe Gln Glu His Thr Val Asp Gly Glu Asn  
 85 90 95  
 Gln Ile Val Phe Thr His Arg Ile Asn Ile Pro Arg Arg Ala Cys Gly  
 100 105 110  
 Cys Ala Ala Ala Pro Asp Val Lys Glu Leu Leu Ser Arg Leu Glu Glu  
 115 120 125  
 Leu Glu Asn Leu Val Ser Ser Leu Arg Glu Gln Cys Thr Ala Gly Ala  
 130 135 140  
 Gly Cys Cys Leu Gln Pro Ala Thr Gly Arg Leu Asp Thr Arg Pro Phe  
 145 150 155 160  
 Cys Ser Gly Arg Gly Asn Phe Ser Thr Glu Gly Cys Gly Cys Val Cys  
 165 170 175  
 Glu Pro Gly Trp Lys Gly Pro Asn Cys Ser Glu Pro Glu Cys Pro Gly  
 180 185 190  
 Asn Cys His Leu Arg Gly Arg Cys Ile Asp Gly Gln Cys Ile Cys Asp  
 195 200 205  
 Asp Gly Phe Thr Gly Glu Asp Cys Ser Gln Leu Ala Cys Pro Ser Asp  
 210 215 220  
 Cys Asn Asp Gln Gly Lys Cys Val Asn Gly Val Cys Ile Cys Phe Glu  
 225 230 235 240  
 Gly Tyr Ala Gly Ala Asp Cys Ser Arg Glu Ile Cys Pro Val Pro Cys  
 245 250 255  
 Ser Glu Glu His Gly Thr Cys Val Asp Gly Leu Cys Val Cys His Asp  
 260 265 270  
 Gly Phe Ala Gly Asp Asp Cys Asn Lys Pro Leu Cys Leu Asn Asn Cys  
 275 280 285  
 Tyr Asn Arg Gly Arg Cys Val Glu Asn Glu Cys Val Cys Asp Glu Gly  
 290 295 300  
 Phe Thr Gly Glu Asp Cys Ser Glu Leu Ile Cys Pro Asn Asp Cys Phe  
 305 310 315 320  
 Asp Arg Gly Arg Cys Ile Asn Gly Thr Cys Tyr Cys Glu Glu Gly Phe  
 325 330 335

Thr Gly Glu Asp Cys Gly Lys Pro Thr Cys Pro His Ala Cys His Thr  
 340 345 350  
 Gln Gly Arg Cys Glu Glu Gly Gln Cys Val Cys Asp Glu Gly Phe Ala  
 355 360 365  
 Gly Leu Asp Cys Ser Glu Lys Arg Cys Pro Ala Asp Cys His Asn Arg  
 370 375 380  
 Gly Arg Cys Val Asp Gly Arg Cys Glu Cys Asp Asp Gly Phe Thr Gly  
 385 390 395 400  
 Ala Asp Cys Gly Glu Leu Lys Cys Pro Asn Gly Cys Ser Gly His Gly  
 405 410 415  
 Arg Cys Val Asn Gly Gln Cys Val Cys Asp Glu Gly Tyr Thr Gly Glu  
 420 425 430  
 Asp Cys Ser Gln Leu Arg Cys Pro Asn Asp Cys His Ser Arg Gly Arg  
 435 440 445  
 Cys Val Glu Gly Lys Cys Val Cys Glu Gln Gly Phe Lys Gly Tyr Asp  
 450 455 460  
 Cys Ser Asp Met Ser Cys Pro Asn Asp Cys His Gln His Gly Arg Cys  
 465 470 475 480  
 Val Asn Gly Met Cys Val Cys Asp Asp Gly Tyr Thr Gly Glu Asp Cys  
 485 490 495  
 Arg Asp Arg Gln Cys Pro Arg Asp Cys Ser Asn Arg Gly Leu Cys Val  
 500 505 510  
 Asp Gly Gln Cys Val Cys Glu Asp Gly Phe Thr Gly Pro Asp Cys Ala  
 515 520 525  
 Glu Leu Ser Cys Pro Asn Asp Cys His Gly Gln Gly Arg Cys Val Asn  
 530 535 540  
 Gly Gln Cys Val Cys His Glu Gly Phe Met Gly Lys Asp Cys Lys Glu  
 545 550 555 560  
 Gln Arg Cys Pro Ser Asp Cys His Gly Gln Gly Arg Cys Val Asp Gly  
 565 570 575  
 Gln Cys Ile Cys His Glu Gly Phe Thr Gly Leu Asp Cys Gly Gln His  
 580 585 590  
 Ser Cys Pro Ser Asp Cys Asn Asn Leu Gly Gln Cys Val Ser Gly Arg  
 595 600 605  
 Cys Ile Cys Asn Glu Gly Tyr Ser Gly Glu Asp Cys Ser Glu Val Ser  
 610 615 620  
 Pro Pro Lys Asp Leu Val Val Thr Glu Val Thr Glu Glu Thr Val Asn  
 625 630 635 640  
 Leu Ala Trp Asp Asn Glu Met Arg Val Thr Glu Tyr Leu Val Val Tyr  
 645 650 655  
 Thr Pro Thr His Glu Gly Gly Leu Glu Met Gln Phe Arg Val Pro Gly  
 660 665 670  
 Asp Gln Thr Ser Thr Ile Ile Gln Glu Leu Glu Pro Gly Val Glu Tyr  
 675 680 685  
 Phe Ile Arg Val Phe Ala Ile Leu Glu Asn Lys Lys Ser Ile Pro Val  
 690 695 700  
 Ser Ala Arg Val Ala Thr Tyr Leu Pro Ala Pro Glu Gly Leu Lys Phe  
 705 710 715 720  
 Lys Ser Ile Lys Glu Thr Ser Val Glu Val Glu Trp Asp Pro Leu Asp  
 725 730 735  
 Ile Ala Phe Glu Thr Trp Glu Ile Ile Phe Arg Asn Met Asn Lys Glu  
 740 745 750  
 Asp Glu Gly Glu Ile Thr Lys Ser Leu Arg Arg Pro Glu Thr Ser Tyr  
 755 760 765  
 Arg Gln Thr Gly Leu Ala Pro Gly Gln Glu Tyr Glu Ile Ser Leu His  
 770 775 780

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Ile Val Lys Asn Asn Thr Arg Gly Pro Gly Leu Lys Arg Val Thr Thr
785                               790                               795                               800

Thr Arg Leu Asp Ala Pro Ser Gln Ile Glu Val Lys Asp Val Thr Asp
                               805                               810                               815

Thr Thr Ala Leu Ile Thr Trp Phe Lys Pro Leu Ala Glu Ile Asp Gly
                               820                               825                               830

Ile Glu Leu Thr Tyr Gly Ile Lys Asp Val Pro Gly Asp Arg Thr Thr
                               835                               840                               845

Ile Asp Leu Thr Glu Asp Glu Asn Gln Tyr Ser Ile Gly Asn Leu Lys
                               850                               855                               860

Pro Asp Thr Glu Tyr Glu Val Ser Leu Ile Ser Arg Arg Gly Asp Met
865                               870                               875                               880

Ser Ser Asn Pro Ala Lys Glu Thr Phe Thr Thr Gly Leu Asp Ala Pro
                               885                               890                               895

Arg Asn Leu Arg Arg Val Ser Gln Thr Asp Asn Ser Ile Thr Leu Glu
                               900                               905                               910

Trp Arg Asn Gly Lys Ala Ala Ile Asp Ser Tyr Arg Ile Lys Tyr Ala
                               915                               920                               925

Pro Ile Ser Gly Gly Asp His Ala Glu Val Asp Val Pro Lys Ser Gln
                               930                               935                               940

Gln Ala Thr Thr Lys Thr Leu Thr Gly Leu Arg Pro Gly Thr Glu
945                               950                               955                               960

Tyr Gly Ile Gly Val Ser Ala Val Lys Glu Asp Lys Glu Ser Asn Pro
                               965                               970                               975

Ala Thr Ile Asn Ala Ala Thr Glu Leu Asp Thr Pro Lys Asp Leu Gln
                               980                               985                               990

Val Ser Glu Thr Ala Glu Thr Ser Leu Thr Leu Leu Trp Lys Thr Pro
                               995                               1000                               1005

Leu Ala Lys Phe Asp Arg Tyr Arg Leu Asn Tyr Ser Leu Pro Thr
1010                               1015                               1020

Gly Gln Trp Val Gly Val Gln Leu Pro Arg Asn Thr Thr Ser Tyr
1025                               1030                               1035

Val Leu Arg Gly Leu Glu Pro Gly Gln Glu Tyr Asn Val Leu Leu
1040                               1045                               1050

Thr Ala Glu Lys Gly Arg His Lys Ser Lys Pro Ala Arg Val Lys
1055                               1060                               1065

Ala Ser Thr Glu Gln Ala Pro Glu Leu Glu Asn Leu Thr Val Thr
1070                               1075                               1080

Glu Val Gly Trp Asp Gly Leu Arg Leu Asn Trp Thr Ala Ala Asp
1085                               1090                               1095

Gln Ala Tyr Glu His Phe Ile Ile Gln Val Gln Glu Ala Asn Lys
1100                               1105                               1110

Val Glu Ala Ala Arg Asn Leu Thr Val Pro Gly Ser Leu Arg Ala
1115                               1120                               1125

Val Asp Ile Pro Gly Leu Lys Ala Ala Thr Pro Tyr Thr Val Ser
1130                               1135                               1140

Ile Tyr Gly Val Ile Gln Gly Tyr Arg Thr Pro Val Leu Ser Ala
1145                               1150                               1155

Glu Ala Ser Thr Gly Glu Thr Pro Asn Leu Gly Glu Val Val Val
1160                               1165                               1170

Ala Glu Val Gly Trp Asp Ala Leu Lys Leu Asn Trp Thr Ala Pro
1175                               1180                               1185

Glu Gly Ala Tyr Glu Tyr Phe Phe Ile Gln Val Gln Glu Ala Asp
1190                               1195                               1200

Thr Val Glu Ala Ala Gln Asn Leu Thr Val Pro Gly Gly Leu Arg
1205                               1210                               1215

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Ser	Thr	Asp	Leu	Pro	Gly	Leu	Lys	Ala	Ala	Thr	His	Tyr	Thr	Ile
1220						1225					1230			
Thr	Ile	Arg	Gly	Val	Thr	Gln	Asp	Phe	Ser	Thr	Thr	Pro	Leu	Ser
1235						1240					1245			
Val	Glu	Val	Leu	Thr	Glu	Glu	Val	Pro	Asp	Met	Gly	Asn	Leu	Thr
1250						1255					1260			
Val	Thr	Glu	Val	Ser	Trp	Asp	Ala	Leu	Arg	Leu	Asn	Trp	Thr	Thr
1265						1270					1275			
Pro	Asp	Gly	Thr	Tyr	Asp	Gln	Phe	Thr	Ile	Gln	Val	Gln	Glu	Ala
1280						1285					1290			
Asp	Gln	Val	Glu	Glu	Ala	His	Asn	Leu	Thr	Val	Pro	Gly	Ser	Leu
1295						1300					1305			
Arg	Ser	Met	Glu	Ile	Pro	Gly	Leu	Arg	Ala	Gly	Thr	Pro	Tyr	Thr
1310						1315					1320			
Val	Thr	Leu	His	Gly	Glu	Val	Arg	Gly	His	Ser	Thr	Arg	Pro	Leu
1325						1330					1335			
Ala	Val	Glu	Val	Val	Thr	Glu	Asp	Leu	Pro	Gln	Leu	Gly	Asp	Leu
1340						1345					1350			
Ala	Val	Ser	Glu	Val	Gly	Trp	Asp	Gly	Leu	Arg	Leu	Asn	Trp	Thr
1355						1360					1365			
Ala	Ala	Asp	Asn	Ala	Tyr	Glu	His	Phe	Val	Ile	Gln	Val	Gln	Glu
1370						1375					1380			
Val	Asn	Lys	Val	Glu	Ala	Ala	Gln	Asn	Leu	Thr	Leu	Pro	Gly	Ser
1385						1390					1395			
Leu	Arg	Ala	Val	Asp	Ile	Pro	Gly	Leu	Glu	Ala	Ala	Thr	Pro	Tyr
1400						1405					1410			
Arg	Val	Ser	Ile	Tyr	Gly	Val	Ile	Arg	Gly	Tyr	Arg	Thr	Pro	Val
1415						1420					1425			
Leu	Ser	Ala	Glu	Ala	Ser	Thr	Ala	Lys	Glu	Pro	Glu	Ile	Gly	Asn
1430						1435					1440			
Leu	Asn	Val	Ser	Asp	Ile	Thr	Pro	Glu	Ser	Phe	Asn	Leu	Ser	Trp
1445						1450					1455			
Met	Ala	Thr	Asp	Gly	Ile	Phe	Glu	Thr	Phe	Thr	Ile	Glu	Ile	Ile
1460						1465					1470			
Asp	Ser	Asn	Arg	Leu	Leu	Glu	Thr	Val	Glu	Tyr	Asn	Ile	Ser	Gly
1475						1480					1485			
Ala	Glu	Arg	Thr	Ala	His	Ile	Ser	Gly	Leu	Pro	Pro	Ser	Thr	Asp
1490						1495					1500			
Phe	Ile	Val	Tyr	Leu	Ser	Gly	Leu	Ala	Pro	Ser	Ile	Arg	Thr	Lys
1505						1510					1515			
Thr	Ile	Ser	Ala	Thr	Ala	Thr	Thr	Glu	Ala	Leu	Pro	Leu	Leu	Glu
1520						1525					1530			
Asn	Leu	Thr	Ile	Ser	Asp	Ile	Asn	Pro	Tyr	Gly	Phe	Thr	Val	Ser
1535						1540					1545			
Trp	Met	Ala	Ser	Glu	Asn	Ala	Phe	Asp	Ser	Phe	Leu	Val	Thr	Val
1550						1555					1560			
Val	Asp	Ser	Gly	Lys	Leu	Leu	Asp	Pro	Gln	Glu	Phe	Thr	Leu	Ser
1565						1570					1575			
Gly	Thr	Gln	Arg	Lys	Leu	Glu	Leu	Arg	Gly	Leu	Ile	Thr	Gly	Ile
1580						1585					1590			
Gly	Tyr	Glu	Val	Met	Val	Ser	Gly	Phe	Thr	Gln	Gly	His	Gln	Thr
1595						1600					1605			
Lys	Pro	Leu	Arg	Ala	Glu	Ile	Val	Thr	Glu	Ala	Glu	Pro	Glu	Val
1610						1615					1620			
Asp	Asn	Leu	Leu	Val	Ser	Asp	Ala	Thr	Pro	Asp	Gly	Phe	Arg	Leu
1625						1630					1635			

Ser	Trp	Thr	Ala	Asp	Glu	Gly	Val	Phe	Asp	Asn	Phe	Val	Leu	Lys
1640						1645					1650			
Ile	Arg	Asp	Thr	Lys	Lys	Gln	Ser	Glu	Pro	Leu	Glu	Ile	Thr	Leu
1655						1660					1665			
Leu	Ala	Pro	Glu	Arg	Thr	Arg	Asp	Leu	Thr	Gly	Leu	Arg	Glu	Ala
1670						1675					1680			
Thr	Glu	Tyr	Glu	Ile	Glu	Leu	Tyr	Gly	Ile	Ser	Lys	Gly	Arg	Arg
1685						1690					1695			
Ser	Gln	Thr	Val	Ser	Ala	Ile	Ala	Thr	Thr	Ala	Met	Gly	Ser	Pro
1700						1705					1710			
Lys	Glu	Val	Ile	Phe	Ser	Asp	Ile	Thr	Glu	Asn	Ser	Ala	Thr	Val
1715						1720					1725			
Ser	Trp	Arg	Ala	Pro	Thr	Ala	Gln	Val	Glu	Ser	Phe	Arg	Ile	Thr
1730						1735					1740			
Tyr	Val	Pro	Ile	Thr	Gly	Gly	Thr	Pro	Ser	Met	Val	Thr	Val	Asp
1745						1750					1755			
Gly	Thr	Lys	Thr	Gln	Thr	Arg	Leu	Val	Lys	Leu	Ile	Pro	Gly	Val
1760						1765					1770			
Glu	Tyr	Leu	Val	Ser	Ile	Ile	Ala	Met	Lys	Gly	Phe	Glu	Glu	Ser
1775						1780					1785			
Glu	Pro	Val	Ser	Gly	Ser	Phe	Thr	Thr	Ala	Leu	Asp	Gly	Pro	Ser
1790						1795					1800			
Gly	Leu	Val	Thr	Ala	Asn	Ile	Thr	Asp	Ser	Glu	Ala	Leu	Ala	Arg
1805						1810					1815			
Trp	Gln	Pro	Ala	Ile	Ala	Thr	Val	Asp	Ser	Tyr	Val	Ile	Ser	Tyr
1820						1825					1830			
Thr	Gly	Glu	Lys	Val	Pro	Glu	Ile	Thr	Arg	Thr	Val	Ser	Gly	Asn
1835						1840					1845			
Thr	Val	Glu	Tyr	Ala	Leu	Thr	Asp	Leu	Glu	Pro	Ala	Thr	Glu	Tyr
1850						1855					1860			
Thr	Leu	Arg	Ile	Phe	Ala	Glu	Lys	Gly	Pro	Gln	Lys	Ser	Ser	Thr
1865						1870					1875			
Ile	Thr	Ala	Lys	Phe	Thr	Thr	Asp	Leu	Asp	Ser	Pro	Arg	Asp	Leu
1880						1885					1890			
Thr	Ala	Thr	Glu	Val	Gln	Ser	Glu	Thr	Ala	Leu	Leu	Thr	Trp	Arg
1895						1900					1905			
Pro	Pro	Arg	Ala	Ser	Val	Thr	Gly	Tyr	Leu	Leu	Val	Tyr	Glu	Ser
1910						1915					1920			
Val	Asp	Gly	Thr	Val	Lys	Glu	Val	Ile	Val	Gly	Pro	Asp	Thr	Thr
1925						1930					1935			
Ser	Tyr	Ser	Leu	Ala	Asp	Leu	Ser	Pro	Ser	Thr	His	Tyr	Thr	Ala
1940						1945					1950			
Lys	Ile	Gln	Ala	Leu	Asn	Gly	Pro	Leu	Arg	Ser	Asn	Met	Ile	Gln
1955						1960					1965			
Thr	Ile	Phe	Thr	Thr	Ile	Gly	Leu	Leu	Tyr	Pro	Phe	Pro	Lys	Asp
1970						1975					1980			
Cys	Ser	Gln	Ala	Met	Leu	Asn	Gly	Asp	Thr	Thr	Ser	Gly	Leu	Tyr
1985						1990					1995			
Thr	Ile	Tyr	Leu	Asn	Gly	Asp	Lys	Ala	Gln	Ala	Leu	Glu	Val	Phe
2000						2005					2010			
Cys	Asp	Met	Thr	Ser	Asp	Gly	Gly	Gly	Trp	Ile	Val	Phe	Leu	Arg
2015						2020					2025			
Arg	Lys	Asn	Gly	Arg	Glu	Asn	Phe	Tyr	Gln	Asn	Trp	Lys	Ala	Tyr
2030						2035					2040			
Ala	Ala	Gly	Phe	Gly	Asp	Arg	Arg	Glu	Glu	Phe	Trp	Leu	Gly	Leu
2045						2050					2055			

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Asp Asn Leu Asn Lys Ile Thr Ala Gln Gly Gln Tyr Glu Leu Arg
2060      2065      2070
Val Asp Leu Arg Asp His Gly Glu Thr Ala Phe Ala Val Tyr Asp
2075      2080      2085
Lys Phe Ser Val Gly Asp Ala Lys Thr Arg Tyr Lys Leu Lys Val
2090      2095      2100
Glu Gly Tyr Ser Gly Thr Ala Gly Asp Ser Met Ala Tyr His Asn
2105      2110      2115
Gly Arg Ser Phe Ser Thr Phe Asp Lys Asp Thr Asp Ser Ala Ile
2120      2125      2130
Thr Asn Cys Ala Leu Ser Tyr Lys Gly Ala Phe Trp Tyr Arg Asn
2135      2140      2145
Cys His Arg Val Asn Leu Met Gly Arg Tyr Gly Asp Asn Asn His
2150      2155      2160
Ser Gln Gly Val Asn Trp Phe His Trp Lys Gly His Glu His Ser
2165      2170      2175
Ile Gln Phe Ala Glu Met Lys Leu Arg Pro Ser Asn Phe Arg Asn
2180      2185      2190
Leu Glu Gly Arg Arg Lys Arg Ala
2195      2200

<210> 137
<211> 326
<212> PRT
<213> Homo sapiens

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Val Leu Phe Leu His Ile Lys Asn Leu Pro Ala Gln Ala Ala Asp Thr
20      25      30
Cys Pro Glu Val Lys Val Val Gly Leu Glu Gly Ser Asp Lys Leu Thr
35      40      45
Ile Leu Arg Gly Cys Pro Gly Leu Pro Gly Ala Pro Gly Pro Lys Gly
50      55      60
Glu Ala Gly Val Ile Gly Glu Arg Gly Glu Arg Gly Leu Pro Gly Ala
65      70      75      80
Pro Gly Lys Ala Gly Pro Val Gly Pro Lys Gly Asp Arg Gly Glu Lys
85      90      95
Gly Met Arg Gly Glu Lys Gly Asp Ala Gly Gln Ser Gln Ser Cys Ala
100      105      110
Thr Gly Pro Arg Asn Cys Lys Asp Leu Leu Asp Arg Gly Tyr Phe Leu
115      120      125
Ser Gly Trp His Thr Ile Tyr Leu Pro Asp Cys Arg Pro Leu Thr Val
130      135      140
Leu Cys Asp Met Asp Thr Asp Gly Gly Gly Trp Thr Val Phe Gln Arg
145      150      155      160
Arg Met Asp Gly Ser Val Asp Phe Tyr Arg Asp Trp Ala Ala Tyr Lys
165      170      175
Gln Gly Phe Gly Ser Gln Leu Gly Glu Phe Trp Leu Gly Asn Asp Asn
180      185      190
Ile His Ala Leu Thr Ala Gln Gly Ser Ser Glu Leu Arg Val Asp Leu
195      200      205
Val Asp Phe Glu Gly Asn His Gln Phe Ala Lys Tyr Lys Ser Phe Lys
210      215      220
Val Ala Asp Glu Ala Glu Lys Tyr Lys Leu Val Leu Gly Ala Phe Val
225      230      235      240
Gly Gly Ser Ala Gly Asn Ser Leu Thr Gly His Asn Asn Asn Phe Phe
245      250      255

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Ser Thr Lys Asp Gln Asp Asn Asp Val Ser Ser Ser Asn Cys Ala Glu  
 260 265 270  
 Lys Phe Gln Gly Ala Trp Trp Tyr Ala Asp Cys His Ala Ser Asn Leu  
 275 280 285  
 Asn Gly Leu Tyr Leu Met Gly Pro His Glu Ser Tyr Ala Asn Gly Ile  
 290 295 300  
 Asn Trp Ser Ala Ala Lys Gly Tyr Lys Tyr Ser Tyr Lys Val Ser Glu  
 305 310 315 320  
 Met Lys Val Arg Pro Ala  
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<210> 138  
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 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> misc feature  
 <222> (269)..(272)  
 <223> "Xaa" may be any amino acid.

<400> 138  
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 Ala Ala Tyr Asn Asn Phe Arg Lys Ser Met Asp Ser Asp Gly Lys Lys  
 20 25 30  
 Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro  
 35 40 45  
 Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala  
 50 55 60  
 Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu  
 65 70 75 80  
 Gln Val Leu Glu Asn Asp Met Glu Asn Asn Thr Gln Trp Leu Met Lys  
 85 90 95  
 Leu Glu Asn Asp Ser Gln Asp Asn Met Lys Lys Glu Met Val Glu Asp  
 100 105 110  
 Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Asp Glu Asp Gly  
 115 120 125  
 Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp  
 130 135 140  
 Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu Leu Gln Leu  
 145 150 155 160  
 Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Asp Leu Asp  
 165 170 175  
 Gln Thr Ser Glu Asp Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu  
 180 185 190  
 Lys Lys Val Leu Ala Met Glu Asp Lys His Asp Asp Gln Leu Gln Ser  
 195 200 205  
 Asp Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn  
 210 215 220  
 Ser Asp Asp Glu Glu Leu Glu Lys Lys Asp Val Thr Ala Thr Val Asn  
 225 230 235 240  
 Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn  
 245 250 255  
 Asn Leu Leu Thr Met Met Ser Thr Ser Asn Cys Lys Xaa Xaa Xaa Xaa  
 260 265 270  
 Val Ala Lys Glu Glu Gln Asp Ser Phe Arg Asp Cys Ala Glu Val Phe  
 275 280 285  
 Lys Ser Gly His Thr Thr Asn Gly Asp Tyr Thr Leu Met Trp Gln Asp  
 290 295 300

Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala Ala Ala Tyr Asn  
305 310 315 320

Asn Phe Arg Lys Ser Met Asp Ser Asp Gly Lys Lys Gln Tyr Gln Val  
325 330 335

Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro Glu Met Asp Asn  
340 345 350

Cys Arg Ser Ser Ser Ser Pro Tyr  
355 360

<210> 139  
<211> 19  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 139

Val Asn Leu Ser Thr Lys Glu Gly Val Leu Leu Lys Gly Lys Arg Glu  
1 5 10 15

Glu Glu Lys

<210> 140  
<211> 4  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 140

Asp Glu Gly Arg  
1

<210> 141  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 141

Gly Gly Gly Gly Ser Ser Ser  
1 5

<210> 142  
<211> 10  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 142

Pro Gly Gly Asp Ser Gly Gly Gly Gly Gly  
1 5 10

<210> 143  
<211> 15  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 143

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
1 5 10 15

<210> 144  
<211> 13  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 144

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Lys Glu Phe  
1 5 10

<210> 145  
<211> 26  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Synthetic

<400> 145

Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu  
1 5 10 15

Val Leu His His Ala Lys Trp Ser Gln Ala  
20 25

<210> 146  
<211> 54  
<212> PRT  
<213> Homo sapiens

<400> 146

Met Thr Val Phe Leu Ser Phe Ala Phe Leu Ala Ala Asp Leu Thr His  
1 5 10 15

Asp Gly Cys Ser Asn Gln Arg Arg Ser Pro Glu Asn Ser Gly Arg Arg  
20 25 30

Tyr Asn Arg Asp Gln His Gly Gln Cys Ala Tyr Thr Phe Asp Leu Pro  
35 40 45

Gln His Asp Gly Asn Cys  
50

<210> 147  
<211> 570  
<212> DNA  
<213> Homo sapiens

<400> 147  
atgccggagc cgaagaaggt gttctgtaac atggacctca acgggggggg gtggaccgtg 60  
atacagcacc gggaggacgg gtcgctcgac ttccagcggg ggtggaagga gtacaagatg 120  
gggttcggga acccgctcggg ggagtactgg ctcggaacg agttcatttt cgccattacc 180  
tcgcagcggc agtacatgct ccggattgag ctcatggact gggaggggaa ccgggcctac 240  
tcgcagtacg accggttcca cataggaac gagaagcaga actaccggct ctacctcaag 300  
gggcacaccg ggaccgccgg gaagcagtcg tcgctcaacc tccacggggc cgacttctcg 360  
accaaggacg ccgacaacga caactgtatg tgtaagtgtg ccctcatgct caccgggggg 420  
tggtggttcg acgcctgtgg gccgtcgaac ctcaacggga tgttctacac cgccgggcag 480  
aaccacggga agctcaacgg gataaagtgg cactacttca aggggccgct gtactcgctc 540  
cggtcgacca ccatgatgat tcggccgctc 570

<210> 148  
<211> 1494  
<212> DNA  
<213> Homo sapiens

<400> 148  
atgacagttt tcctttcctt tgctttcctc gctgccatc tgactcacat aggggtgcagc 60  
aatcagcgcc gaagtccaga aaacagtggg agaagatata accggattca acatgggcaa 120  
tgtgcctaca ctttcattct tccagaacac gatggcaact gtcgtgagag tacgacagac 180  
cagtacaaca caaacgctct gcagagagat gctccacacg tggaaccgga tttctcttcc 240

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cagaaacttc aacatctgga acatgtgatg gaaaattata ctcagtggct gcaaaaactt 300
gagaattaca ttgtggaaaa catgaagtcg gagatggccc agatacagca gaatgcagtt 360
cagaaccaca cggctaccat gctggagata ggaaccagcc tcctctctca gactgcagag 420
cagaccagaa agctgacaga tgttgagacc caggtactaa atcaaacttc tcgacttgag 480
atacagctgc tggagaattc attatccacc tacaagctag agaagcaact tcttcaacag 540
acaaatgaaa tcttgaagat ccatgaaaaa aacagtttat tagaacataa aatcttagaa 600
atggaaggaa aacacaagga agagtggac accttaaagg aagagaaaga gaaccttcaa 660
ggcttggtta ctctgcaaac atatataatc caggagctgg aaaagcaatt aaacagagct 720
accaccaaca acagtgtcct tcagaagcag caactggagc tgatggacac agtccacaac 780
cttgtcaatc ttgtcactaa agaagggtgt ttactaaagg gaggaaaaag agaggaagag 840
aaaccattta gagactgtgc agatgtatat caagctggtt ttaataaaag tggaatctac 900
actatttata ttaataatat gccagaaccc aaaaagggtgt tttgcaatat ggatgtcaat 960
gggggagggt ggactgtaat acaacatcgt gaagatggaa gtctagattt ccaaaggagg 1020
tggaaggaa ataaaatggg ttttgaaat ccctccggtg aatattggct ggggaatgag 1080
tttatttttg ccattaccag tcagaggcag tacatgctaa gaattgagtt aatggactgg 1140
gaagggaaac gagcctattc acagtatgac agattccaca taggaaatga aaagcaaac 1200
tataggttgt atttaaaagg tcacactggg acagcaggaa aacagagcag cctgatctta 1260
cacggtgctg atttcagcac taaagatgct gataatgaca actgtatgtg caaatgtgcc 1320
ctcatgttaa caggaggatg gtggtttgat gcttgtggcc cctccaatct aaatggaatg 1380
ttctatactg cgggacaaaa ccatggaaaa ctgaatggga taaagtggca ctacttcaaa 1440
gggccagtt actccttacg ttccacaact atgatgattc gacctttaga tttt 1494

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```

<210> 149
<211> 1494
<212> DNA
<213> Homo sapiens

```

```

<400> 149
atgacagttt tcctttcctt tgctttcctc gctgccattc tgactcacat aggggtgcagc 60
aatcagcgcc gaagtccaga aaacagtggg agaagatata accggattca acatgggcaa 120
tgtgcctaca ctttcattct tccagaacac gatggcaact gtcgtgagag tacgacagac 180
cagtacaaca caaacgctct gcagagagat gctccacacg tggaaaccgga tttctcttcc 240
cagaaacttc aacatctgga acatgtgatg gaaaattata ctcagtggct gcaaaaactt 300
gagaattaca ttgtggaaaa catgaagtcg gagatggccc agatacagca gaatgcagtt 360
cagaaccaca cggctaccat gctggagata ggaaccagcc tcctctctca gactgcagag 420
cagaccagaa agctgacaga tgttgagacc caggtactaa atcaaacttc tcgacttgag 480
atacagctgc tggagaattc attatccacc tacaagctag agaagcaact tcttcaacag 540
acaaatgaaa tcttgaagat ccatgaaaaa aacagtttat tagaacataa aatcttagaa 600
atggaaggaa aacacaagga agagtggac accttaaagg aagagaaaga gaaccttcaa 660
ggcttggtta ctctgcaaac atatataatc caggagctgg aaaagcaatt aaacagagct 720
accaccaaca acagtgtcct tcagaagcag caactggagc tgatggacac agtccacaac 780
cttgtcaatc ttgtcactaa agaagggtgt ttactaaagg gaggaaaaag agaggaagag 840
aaaccattta gagactgtgc agatgtatat caagctggtt ttaataaaag tggaatctac 900
actatttata ttaataatat gccagaaccc aaaaagggtgt tttgcaatat ggatgtcaat 960
gggggagggt ggactgtaat acaacatcgt gaagatggaa gtctagattt ccaaaggagg 1020
tggaaggaa ataaaatggg ttttgaaat ccctccggtg aatattggct ggggaatgag 1080

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tttatttttg ccattaccag tcagaggcag tacatgctaa gaattgagtt aatggactgg 1140
gaagggaacc gagcctattc acagtatgac agattccaca taggaaatga aaagcaaaac 1200
tatagggttg atttaaaagg tcacactggg acagcaggaa aacagagcag cctgatctta 1260
cacggtgctg atttcagcac taaagatgct gataatgaca actgtatgtg caaatgtgcc 1320
ctcatgttaa caggaggatg gtggtttgat gcttgtggcc cctccaatct aaatggaatg 1380
ttctatactg cgggacaaaa ccatggaaaa ctgaatggga taaagtggca ctacttcaaa 1440
gggcccagtt actccttacg ttccacaact atgatgattc gacctttaga tttt 1494

```

```

<210> 150
<211> 570
<212> DNA
<213> Homo sapiens

```

```

<400> 150
atgccagaac ccaaaaaggt gttttgcaat atggatgtca atgggggagg ttggactgta 60
atacaacatc gtgaagatgg aagtctagat ttccaaagag gctggaagga atataaaatg 120
ggtttttgaa atccctccgg tgaatattgg ctggggaatg agtttatttt tgccattacc 180
agtcagaggc agtacatgct aagaattgag ttaatggact gggaagggaa ccgagcctat 240
tcacagtatg acagattcca cataggaaat gaaaagcaaa actatagggt gtatttaaaa 300
ggtcacactg ggacagcagg aaaacagagc agcctgatct tacacggtgc tgatttcagc 360
actaaagatg ctgataatga caactgtatg tgcaaatgtg ccctcatgtt aacaggagga 420
tggtggtttg atgcttgtgg cccctccaat ctaaatggaa tgttctatac tgcgggacaa 480
aaccatggaa aactgaatgg gataaagtgg cactacttca aaggggccag ttactcctta 540
cgttccacaa ctatgatgat tcgaccttta 570

```

```

<210> 151
<211> 732
<212> DNA
<213> Homo sapiens

```

```

<400> 151
tgtgatcttg tcttggccgc agcctataac aactttcgga agagcatgga cagcatagga 60
aagaagcaat atcagggtcca gcattgggtcc tgcagctaca ctttcctcct gccagagatg 120
gacaactgcc gctcttcctc cagccctac gtgtccaatg ctgtgcagag ggacgcgccg 180
ctcgaatacg atgactcggg gcagaggctg caagtgtctg agaacatcat ggaaaacaac 240
actcagtggc taatgaagct tgagaattat atccaggaca acatgaagaa agaaatggta 300
gagatacagc agaatgcagt acagaaccag acggctgtga tgatagaaat agggacaaac 360
ctgttgaaac aaacagctga gcaaacgcgg aagttaactg atgtggaagc ccaagtatta 420
aatcagacca cgagacttga acttcagctc ttggaacact ccctctcgac aaacaaattg 480
gaaaaacaga ttttggaacca gaccagtga ataaacaaat tgcaagataa gaacagtttc 540
ctagaaaaga aggtgctagc tatggaagac aagcacatca tccaactaca gtcaataaaa 600
gaagagaaag atcagctaca ggtgttagta tccaagcaaa attccatcat tgaagaacta 660
gaaaaaaaaa tagtgactgc cacggtgaat aattcagttc ttcaaaagca gcaacatgat 720
ctcatggaga ca 732

```

```

<210> 152
<211> 652
<212> DNA
<213> Homo sapiens

```

```

<400> 152
aagccgtcgg gcccatggag agactgcctg caggccctgg aggatggcca cgacaccagc 60
tccatctacc tggatgaagc ggagaacacc aaccgcctca tgcaggtgtg gtgcgaccag 120
agacacgacc ccgggggctg gaccgtcatc cagagacgcc tggatggctc tgttaacttc 180

```



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ttcaggaact gggagacgta caagcaaggg tttgggaaca ttgacggcga atactggctg 240
ggcctggaga acatttactg gctgacgaac caaggcaact acaaactcct ggtgaccatg 300
gaggactggg ccggccgcaa agtctttgca gaatacgcca gtttccgcct ggaacctgag 360
agcgagtatt ataagctgcg gctggggcgc taccatggca atgcgggtga ctcttttaca 420
tggcacaacg gcaagcagtt caccaccctg gacagagatc atgatgtcta cacaggaaac 480
tgtgcccact accagaaggg aggctgggtg tataccactc caacctcaac ggggtctggg 540
accgcggggg ccatgctacc aggacggagt ctactgggct gagttccgag gaggctctta 600
ctcactcaag aaagtgggtg tgatgatccg accgaacccc aacaccttcc ac 652

```

```

<210> 153
<211> 660
<212> DNA
<213> Homo sapiens

```

```

<400> 153
atcaatgaag gaccattcaa agactgtcag caagcaaaag aagctgggca ttcggtcagt 60
gggatttata tgattaaacc tgaaaacagc aatggaccaa tgcagttatg gtgtgaaaac 120
agtttgacc ctgggggttg gactgttatt cagaaaagaa cagacggctc tgtcaacttc 180
ttcagaaatt gggaaaatta taagaaaggg tttggaaaca ttgacggaga atactggctt 240
ggactggaaa atatctatat gcttagcaat caagataatt acaagttatt gattgaatta 300
gaagactgga gtgataaaaa agtctatgca gaatacagca gctttcgtct ggaacctgaa 360
agtgaattct atagactgcg cctgggaact taccagggaa atgcagggga ttctatgatg 420
tggcataatg gtaaacaatt caccacactg gacagagata aagatatgta tgcaggaaac 480
tgcgccact ttcataaagg aggctgggtg tacaatgcct gtgcacattc taacctaaat 540
ggagtatggg acagaggagg ccattacaga agcaagcacc aagatggaat tttctgggcc 600
gaatacagag gcgggtcata ctcttaaga gcagttcaga tgatgatcaa gcctattgac 660

```

```

<210> 154
<211> 1957
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (1497)..(1497)
<223> "n" may be any nucleotide.

```

```

<400> 154
ggtgcagctg caggcaagcc tggccactgt tggctgcagc aggacatccc aggcacagcc 60
cctaggggctc tgagcagaca tccctcgcca ttgacacatc ttcagatgct ctcccaacta 120
gccatgtctg agggcagcct cctccttggt gttgccacca tgtctgtggc tcaacagaca 180
aggcaggagg cggatagggg ctgcgagaca cttgtagtcc agcacggcca ctgtagctac 240
accttcttgc tgcccaagtc tgagccctgc cctccggggc ctgaggctctc cagggactcc 300
aacaccctcc agagagaatc actggccaac cactgcacc tggggaagtt gccacccag 360
cagggtgaaac agctggagca ggcactgcag aacaacacgc agtggctgaa gaagctagag 420
agggccatca agacgatctt gaggtcgaag ctggagcagg tccagcagca aatggcccag 480
aatcagacgg ccccatgct agagctgggc accagcctcc tgaaccagac cactgccag 540
atccgcaagc tgaccgacat ggagggtcag ctctgaacc agacatcaag aatggatgcc 600
cagatgccag agacctttct gtccaccaac aagctggaga accagctgct gctacagagg 660
cagaagctcc agcagcttca gggccaaaac agcgcgctcg agaagcgggt gcaggccctg 720
gagaccaagc agcaggagga gctggccagc atcctcagca agaaggcgaa gctgctgaac 780
acgctgagcc gccagagcgc cgccctcacc aacatcgagc gcggcctgcg cgggtgcagg 840
cacaactcca gcctcctgca ggaccagcag cacagcctgc gccagctgct ggtgttggtg 900

```

```

cggcacctgg tgcaagaaag ggctaacgcc tcggccccgg ccttcataat ggcaggtgag 960
caggtgttcc aggactgtgc agagatccag cgctctgggg ccagtgccag tgggtgtgtac 1020
accatccagg tgtccaatgc aacgaagccc aggaaggtgt tctgtgacct gcagagcagt 1080
ggaggcaggt ggaccctcat ccagcgccgt gagaatggca ccgtgaattt tcagcggaac 1140
tggaaggatt acaaacaggg cttcggagac ccagctgggg agcactggct gggcaatgaa 1200
gtggtgcacc agctcaccag aagggcagcc tactctctgc gtgtggagct gcaagactgg 1260
gaaggccacg aggcctatgc ccagtacgaa catttcacc tgggcagtga gaaccagcta 1320
tacaggcttt ctgtggtcgg gtacagcggc tcagcagggc gccagagcag cctggctctg 1380
cagaacacca gcttttagcac ccttgactca gacaacgacc actgtctctg caagtgtgcc 1440
caagtgtatg ctggagggtg gtggtttgac gcctgtggcc tgtcaaacct caacggngtc 1500
tactaccacg ctcccgacaa caagtacaag atggacggca tccgtggca ctacttcaag 1560
ggccccagct actcactgcy tgcctctcgc atgatgatac ggccctttgga catctaacga 1620
gcagctgtgc cagaggctgg accacacagg agaagctcgg acttggcact cctggacaac 1680
ctggacccag atgcaagaca ctgtgccacc gccttccctg acaccctggg cttcctgagc 1740
cagccctcct tgacccagaa gtccagaagg gtcatctgcc ccccaactcc cctccgtctg 1800
tgacatggag ggtgttcggg gcccatccct ctgatgtagt cctcgccctt cttctctccc 1860
tcccccttca ggggctccct gcctgagggt cacagtacct tgaatgggct gagaacagac 1920
caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 1957

```

```

<210> 155
<211> 1512
<212> DNA
<213> Homo sapiens

```

```

<400> 155
catgctctcc cagctagcca tgctgcaggg cagcctcctc cttgtggttg ccaccatgtc 60
tgtggctcaa cagacaaggc aggaggcgga taggggctgc gagacacttg tagtccagca 120
cggccactgt agctacacct tcttgctgcc caagtctgag ccctgccctc cggggcctga 180
ggtctccagg gactccaaca cctccagag agaatactg gccaaaccac tgcacctggg 240
gaagttgccc acccagcagg tgaacagct ggagcaggca ctgcagaaca acacgcagtg 300
gctgaagaag ctagagaggg ccataagac gatcttgagg tcgaagctgg agcaggtcca 360
gcagcaaatg gcccagaatc agacggcccc catgctagag ctgggcacca gcctcctgaa 420
ccagaccact gcccagatcc gcaagctgac cgacatggag gctcagctcc tgaaccagac 480
atcaagaatg gatgcccaga tgccagagac ctttctgtcc accaacaagc tggagaacca 540
gctgctgcta cagaggcaga agctccagca gcttcagggc caaaacagcg cgctcgagaa 600
gcggttgtag gccctggaga ccaagcagca ggaggagctg gccagcatcc tcagcaagaa 660
ggcgaagctg ctgaacacgc tgagccgcca gagcgccgcc ctcaccaaca tcgagcgagg 720
cctgcgcggt gtcaggcaca actccagcct cctgcaggac cagcagcaca gcctgcgcca 780
gctgctgggt ttgttgccgc acctggtgca agaaagggct aacgcctcgg ccccgccctt 840
cataatggca ggtgagcagg tgttccagga ctgtgcagag atccagcgct ctggggccag 900
tgccagtggg gtctacacca tccaggtgtc caatgcaacg aagcccagga aggtgttctg 960
tgacctgag agcagtggag gcaggtggac cctcatccag cgccgtgaga atggcaccgt 1020
gaattttcag cggaactgga aggattacaa acagggttc ggagaccag ctggggagca 1080
ctggctgggc aatgaagtgg tgcaccagct caccagaagg gcagcctact ctctgcgtgt 1140
ggagctgcaa gactgggaag gccacgaggc ctatgccag tacgaacatt tccacctggg 1200
cagtgaagac cagctatata ggctttctgt ggtcgggtac agcggtcag cagggcgcca 1260

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gagcagcctg gtccctgcaga acaccagctt tagcaccctt gactcagaca acgaccactg 1320  
 tctctgcaag tgtgccccagg tgatgtcttg aggggtggtgg tttagcgcct gtggcctgtc 1380  
 aaacctcaac ggctgtctact accacgctcc cgacaacaag tacaagatgg acggcatccg 1440  
 ctggcactac ttcaagggcc ccagctactc actgcgtgcc tctcgcctga tgatacggcc 1500  
 tttagacatc ta 1512

<210> 156  
 <211> 1879  
 <212> DNA  
 <213> Homo sapiens

<400> 156  
 gagaagccga gctgagcggg tcctcacacg actgtgatcc gattctttcc agcggcttct 60  
 gcaaccaagc gggctcttacc cccggctcctc cgcgtctcca gtcctcgcac ctggaacccc 120  
 aacgtccccc agagtccccg aatccccgct cccaggctac ctaagaggat gagcgggtgct 180  
 ccgacggccg gggcagccct gatgtctctgc gccgccaccg ccgtgctact gagcgtctcag 240  
 ggcggaccgg tgcagtccaa gtcgcgcgcg tttgcgtcct gggacgagat gaatgtcctg 300  
 gcgcacggac tcctgcagct cggccagggg ctgcgcgaac acgcggagcg caccgcagct 360  
 cagctgagcg cgtctggagcg gcgcctgagc gcgtgctggg ccgcctgtca gggaaccgag 420  
 gggccaccg acctcccgtt agccccctgag agccgggtgg accctgaggt ccttcacagc 480  
 ctgcagacac aactcaaggc tcagaacaac aggatccagc aactcttcca caaggtggcc 540  
 cagcagcagc ggcacctgga gaagcagcac ctgcgaattc agcatctgca aagccagttt 600  
 ggcctcctgg accacaagca cctagaccat gaggtggcca agcctgcccg aagaaagagg 660  
 ctgcccgaga tggcccagcc agttgacctg gtcacaaatg tcagccgcct gcaccggctg 720  
 cccaggagatt gccaggagct gttccagggt ggggagaggc agagtggact atttgaaatc 780  
 cagcctcagg ggtctccgcc atttttggtg aactgcaaga tgacctcaga tggaggcttg 840  
 acagtaattc agaggcgcca cgtgggtca gtggacttca accggccctg ggaaacctac 900  
 aaggcggggg ttggggatcc ccacggcgag ttctggctgg gtctggagaa ggtgcatagc 960  
 atcacggggg accgcaacag ccgcctggcc gtgcagctgc gggactggga tggcaacgcc 1020  
 gagttgtctg agttctccgt gcacctgggt ggcgaggaca cggcctatag cctgcagctc 1080  
 actgcacccg tggccggcca gctgggcgcc accaccgtcc caccagcgg cctctccgta 1140  
 ccttcttcca cttgggacca ggatcacgac ctccgcaggg acaagaactg cgccaagagc 1200  
 ctctctggag gctgggtggt tggcacctgc agccattcca acctcaacgg ccagtacttc 1260  
 cgctccatcc cacagcagcg gcagaagctt aagaagggaa tcttctggaa gacctggcg 1320  
 ggccgctact acccgctgca gggccaccac atgttgatcc agcccatggc agcagaggca 1380  
 gcctcctagc gtccctggctg ggcctggtcc caggccacg aaagacgggt actcttggt 1440  
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cggagcgcac ccgcgtgga gcggcgcctg agcgcgtgcg ggtccgccgg ggtccaccga      300
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<213> Homo sapiens

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<213> Homo sapiens

<400> 164  
gaaattgaaa atcaagataa aaatgttcac aattaattgt tcctctagtt atttctcca 60  
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caatggcctc cttcagttgg gacattgtcc ataagacgaa gggccaaatt aatgacatat 180  
atatttgatc agtcttttta tgatctatcg ctgcaaagaa gaagaaaagg aactgagaag 240  
aactacatat aaatgaagag gtaagaata tgtcacttga actcaactct cctagaagaa 300  
aaaattctac ttcaacaaaa agtggcaact aactaactta attcaaaatc aacctgaaac 360  
aagtaacttc acttaaaact tttgtagaaa aacaaggacc ttctccagac cgtggaagac 420  
caatataaac aatagtcaaa taaaagaaat agaaaatcag ctcaagaa cccacagaaa 480  
tttctctatc ttccaagcca agagcccttt cttcagttga atgaaataag aaatgtaaaa 540

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tgctgaatgt accaccattt ataacagagg tgaacaatgc catcagaccc agcaactctc 600
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aacgtgggag aactacaaat atggatggag aattttggtt gggcctagag aagatatact 720
tctaattatg ttttacgaat tgagttggaa gactgggtat attgaatatt ctttttactt 780
gggaaatcac gatacatcta gttgcgatta ctggcaatgt cccaatgaa agatttggtg 840
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atagattttt tttatcttaa agtcactgtc tatttaatca cataacctta aagaataaccg 1140
tttacatttc tctaatacta tttgttttaa attttgtgat gtgggaatca caatctagat 1200
tataatcaat aggtgaactt attaataaaa aatttagaga cttttattttt aaaaggcatc 1260
cacaactttc ccagtttaaa aaactagtag tcttgttgac taaatacaga ggactggtaa 1320
ttgtacagtt ctttaatttc aaaactaaaa atcgtcagca cagagtataa tacaattttt 1380
taaactgatg cttcattttg ctactaaatg tttgatatga tttatttatg aaacctaag 1440
tgtattaaaa taagttcgct gtcttt 1466

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<210> 165
<211> 1780
<212> DNA
<213> Homo sapiens

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<400> 165
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cgcgtgctca acgcgtccgc cgaggctcag cgcgcagccg cccggttcca ccagctggac 600
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gagcgctgt gcccgggagg cgcgggcggg cagcagcagg tcctgccgcc accccactg 720
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ccagccccag agccccagag agaccagacc cagagacagc aggagcccat ggcttctccc 840
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gaggcccgcc aggcaggcca tgaacagagt ggagtgtatg aactgcgagt gggccgtcac 960
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cggccagacg gagaatactg gctgggcctt gaaccctgtg atcagctgac cagccgtggg 1140
gaccatgagc tgctggttct cctggaggac tggggggggc gtggagcacg tgcccactat 1200
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ggtgatgctg gagactctct ttcctggcac aatgacaagc ccttcagcac cgtggatagg 1320
gaccgagact cctattctgg taactgtgcc ctgtaccagc ggggaggctg gtggtaccat 1380

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gcctgtgcc actccaacct caacgggtgtg tggcaccacg gcggccacta ccgaagcgcg 1440
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gccatgctca ttcgccccct gaagctgtga ctctgtgttc ctctgtcccc taggccctag 1560
aggacattgg tcagcaggag cccaagttgt tctggccaca ctttctttgt ggctcagtgc 1620
caatgtgtcc cacagaactt cccactgtgg atctgtgacc ctgggcgctg aaaatgggac 1680
ccaggaatcc ccccgctcaa tatcttgcc tcagatggct cccaaggtc attcatatct 1740
cggtttgagc tcatatctta taataacaca aagtagccac 1780

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<210> 166
<211> 2042
<212> DNA
<213> Homo sapiens

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<400> 166
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ctatctccag agccaaaatc aagatttgct atgttagacg atgtaaaaat tttagccaat 180
ggcctccttc agttgggaca tggctttaa gactttgtcc ataagacgaa gggccaaatt 240
aatgacatat ttcaaaaact caacatattt gatcagtcct tttatgatct atcgctgcaa 300
accagtgaag tcaaagaaga agaaaaggaa ctgagaagaa ctacatataa actacaagtc 360
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gaagaaaaaa ttctacttca acaaaaagtg aaatathtag aagagcaact aactaactta 480
attcaaaatc aacctgaaac tccagaacac ccagaagtaa cttcacttaa aacttttgta 540
gaaaaacaag ataatagcat caaagacctt ctccagaccg tggaagacca atataaaca 600
ttaaccaaac agcatagtca aataaaagaa atagaaaatc agctcagaag gactagtatt 660
caagaacca cagaaatttc tctatcttcc aagccaagag caccaagaac tactcccttt 720
cttcagttga atgaaataag aaatgtaaaa catgatggca ttctgtctga atgtaccacc 780
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taaaactcta aacttgacta aatacagagg actggtaatt gtacagttct taaatgttgt 1860
agtattaatt tcaaaactaa aaatcgctcag cacagagtat gtgtaaaaat ctgtaataca 1920

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aatttttaaa ctgatgcttc attttgctac aaaataattt ggagtaaag tttgatatga 1980  
 tttatttatg aaacctaag aagcagaatt aaatactgta ttaaaataag ttcgctgtct 2040  
 tt 2042

<210> 167  
 <211> 1858  
 <212> DNA  
 <213> Homo sapiens

<400> 167  
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 ccgttagccc ctgagacgcg ggtggacctt gaggtccttc acacgctgca gacacaactc 480  
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 gccaatggta tctgggcgga gctcacagag ttcttggaaat aaaagcaacc tcagaaca 1858

<210> 168  
 <211> 2148  
 <212> DNA  
 <213> Homo sapiens

<400> 168  
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<210> 169  
 <211> 22  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Synthetic

<400> 169  
 agtaatgcag tccaaagaga cg

22

<210> 170  
 <211> 23  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Synthetic  
 <400> 170  
 aaagtctagt ggttcgatca tca  
 <210> 171  
 <211> 119  
 <212> PRT  
 <213> Artificial Sequence

23

<220>  
 <223> Synthetic  
 <400> 171  
 Ser Asn Ala Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val  
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 Gln Arg Leu Gln Val Leu Glu Asn Asp Met Glu Asn Asn Thr Gln Trp  
 20 25 30  
 Leu Met Lys Leu Glu Asn Asp Ser Gln Asp Asn Met Lys Lys Glu Met  
 35 40 45  
 Val Glu Asp Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Asp  
 50 55 60  
 Glu Asp Gly Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys  
 65 70 75 80  
 Leu Thr Asp Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu  
 85 90 95  
 Leu Gln Leu Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln  
 100 105 110  
 Asp Leu Asp Gln Thr Ser Glu  
 115

<210> 172  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Synthetic  
 <400> 172  
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 Met Glu Asn Asn Thr Gln Trp Leu Met Lys Leu Glu Asn Asp Ser Gln  
 20 25 30  
 Asp Asn Met Lys Lys Glu Met Val Glu Asp Gln Gln Asn Ala Val Gln  
 35 40 45  
 Asn Gln Thr Ala Val Met Asp Glu Asp Gly Thr Asn Leu Leu Asn Gln  
 50 55 60  
 Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp Val Glu Ala Gln Val Ser  
 65 70 75 80  
 Asn Ala Thr Thr Arg Leu Glu Leu Gln Leu Leu Glu His Ser Leu Ser  
 85 90 95  
 Thr Asn Lys Leu Glu Lys Gln Asp Leu Asp Gln Thr Ser Glu  
 100 105 110

<210> 173  
 <211> 981  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Synthetic  
 <400> 173  
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 acgcaatggc tcatgaaatt agagaatatc tcacaggaca atatgaaaaa ggaaatggta 120

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gaaatccaac aaaatgctgt tcaaaaccag acagcagtca tgattgagat aggaacaaac   180
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aacgccacca ctagattgga actacaatta ttagagcatt ccttaagtac aaacaagcta   300
gaaaagcaga ttctggatca aacgtcggag cccttcagag attgtgcaga tgtctatcaa   360
gctgggttta acaagagtgg gatttatacg atttacatta acaatatgcc aggcccaaag   420
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atgatcgaac cactagactt t                                           981

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<210> 174
<211> 360
<212> PRT
<213> Homo sapiens

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<220>
<221> MISC FEATURE
<222> (269)..(272)
<223> "Xaa" may be any amino acid.

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<400> 174

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20         25
Gln Tyr Gln Val Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro
35         40         45
Glu Met Asp Asn Cys Arg Ser Ser Ser Ser Pro Tyr Val Ser Asn Ala
50         55         60
Val Gln Arg Asp Ala Pro Leu Glu Tyr Asp Asp Ser Val Gln Arg Leu
65         70         75
Gln Val Leu Glu Asn Ile Met Glu Asn Asn Thr Gln Trp Leu Met Lys
85         90         95
Leu Glu Asn Ile Ser Gln Asp Asn Met Lys Lys Glu Met Val Glu Ile
100        105        110
Gln Gln Asn Ala Val Gln Asn Gln Thr Ala Val Met Ile Glu Ile Gly
115        120        125
Thr Asn Leu Leu Asn Gln Thr Ala Glu Gln Thr Arg Lys Leu Thr Asp
130        135        140
Val Glu Ala Gln Val Ser Asn Ala Thr Thr Arg Leu Glu Leu Gln Leu
145        150        155        160
Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp
165        170        175
Gln Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu
180        185        190
Lys Lys Val Leu Ala Met Glu Asp Lys His Ile Ile Gln Leu Gln Ser
195        200        205
Ile Lys Glu Glu Lys Asp Gln Leu Gln Val Leu Val Ser Lys Gln Asn
210        215        220

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Ser Ile Ile Glu Glu Leu Glu Lys Lys Ile Val Thr Ala Thr Val Asn  
 225 230 235 240  
 Asn Ser Val Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn  
 245 250 255  
 Asn Leu Leu Thr Met Met Ser Thr Ser Asn Cys Lys Xaa Xaa Xaa Xaa  
 260 265 270  
 Val Ala Lys Glu Glu Gln Ile Ser Phe Arg Asp Cys Ala Glu Val Phe  
 275 280 285  
 Lys Ser Gly His Thr Thr Asn Gly Ile Tyr Thr Leu Met Trp Gln Ile  
 290 295 300  
 Val Phe Phe Thr Leu Ser Cys Asp Leu Val Leu Ala Ala Ala Tyr Asn  
 305 310 315 320  
 Asn Phe Arg Lys Ser Met Asp Ser Ile Gly Lys Lys Gln Tyr Gln Val  
 325 330 335  
 Gln His Gly Ser Cys Ser Tyr Thr Phe Leu Leu Pro Glu Met Asp Asn  
 340 345 350  
 Cys Arg Ser Ser Ser Ser Pro Tyr  
 355 360